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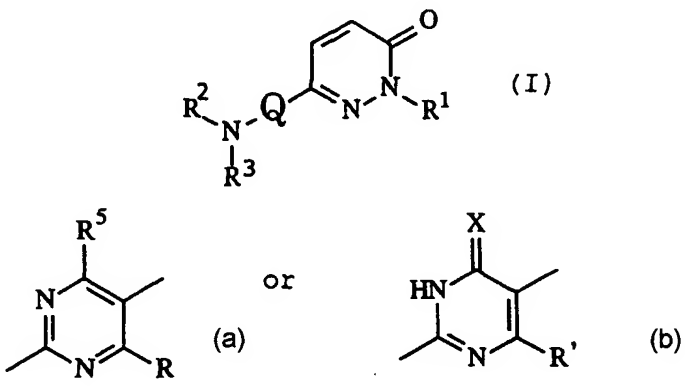
(54) Title: AMINOPYRIMIDINE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abstract: An aminopyrimidine compound of the following formula (I). wherein Q is (a) or (b) in which R and R' are each optionally substituted aryl or heterocyclic group,R^5 is hydrogen, halogen, lower alkyl,optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl, and X is oxygen or sulfur; R^1 is hydrogen, optionally substituted lower alkyl or cyclo (lower) alkyl which may be interrupted by an oxygen atom; R^2 and R^3 are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group; or a salt thereof. The aminopyrimidine compound (I) and salt thereof of the present invention are adenosine antagonists and are useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure and the like.

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AMINOPYRIMIDINE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

TECHNICAL FIELD

The present invention relates to a novel aminopyrimidine compound and a salt thereof, which are useful as medicaments.

BACKGROUND ART

2-Amino-4-aryl-5-(6-oxo-1,6-dihydro-pyridazin-3-yl)-pyrimidine compounds and derivatives thereof are novel, so there has been no knowledge about these compounds. In addition, any aminopyrimidine compounds having both of adenosine A_1 and A_{2a} inhibitory activities are not known.

DISCLOSURE OF INVENTION

The present invention relates to a novel aminopyrimidine compound and a pharmaceutically acceptable salt thereof, which are useful as medicaments; processes for the preparation of said aminopyrimidine compound and a salt thereof; a pharmaceutical composition comprising, as an active ingredient, said aminopyrimidine compound or a pharmaceutically acceptable salt thereof; a use of said aminopyrimidine compound or a pharmaceutically acceptable salt thereof as a medicament; and a method for using said aminopyrimidine compound or a pharmaceutically acceptable salt thereof for therapeutic purposes, which comprises administering said aminopyrimidine compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

The aminopyrimidine compound and a salt thereof are adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action, cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action, etc.), the action of increasing the renal

blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, or the like.

They are useful as cognitive enhancer, antianxiety drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia; drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, or the like;

and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure;

hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.);

circulatory insufficiency (acute circulatory insufficiency) cuased by, for example, ischemia/reperfusion injury (e.g. myocardial ischemia/reperfusion injury, cerebral

ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock, etc.), surgical procedure, or the like; post-resuscitation asystole;

bradyarrhythmia;

electro-mechanical dissociation;

hemodynamic collapse;

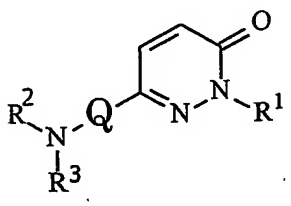
SIRS (systemic inflammatory response syndrome);

multiple organ failure;

renal failure (renal insufficiency) (e.g. acute renal failure, etc.), renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP-0184162), cyclosporin (e.g. cyclosporin A) or the like; glycerol, etc.], nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.); obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.), pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and

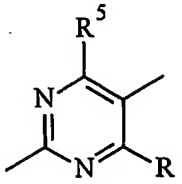
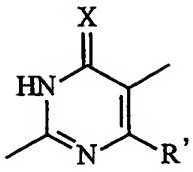
myocardial infarction, thrombosis (e.g. arterial thrombosis, cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, or the like.

The novel aminopyrimidine compound of the present invention can be shown by the following formula (I).



(I)

wherein

Q is  or  ;

in which

R and R′ are each optionally substituted aryl or heterocyclic group,

R^5 is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl, and

X is oxygen or sulfur;

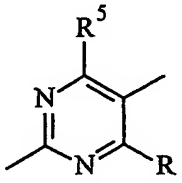
R^1 is hydrogen, optionally substituted lower alkyl or cyclo(lower)alkyl which may be interrupted by an oxygen atom;

R^2 and R^3 are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

or a salt thereof.

The preferred embodiments of the aminopyrimidine compound of the present invention represented by the general formula (I) are as follows.

(1) The aminopyrimidine compound of the general formula (I) wherein

Q is 

in which R and R^5 are each as defined above,

R^1 is optionally substituted lower alkyl, and

R^2 and R^3 are defined above.

(2) The aminopyrimidine compound of (1) above wherein

R^1 is lower alkyl or lower alkoxy(lower)alkyl, and

R^5 is hydrogen.

(3) The aminopyrimidine compound of (2) above wherein

R^1 is lower alkyl, and

R^2 is hydrogen.

(4) The aminopyrimidine compound of the general formula (I) wherein

R^1 is hydrogen, lower alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl or phenyl(lower)alkyl,

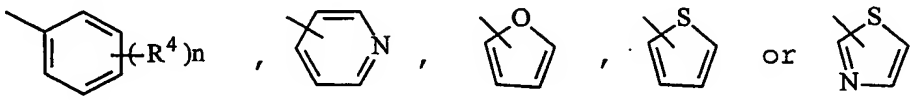
R^2 is hydrogen, lower alkyl, lower alkanoyl or optionally substituted benzoyl,

R^3 is hydrogen, lower alkyl, phenyl, pyridinyl(lower)alkyl or $-CO-R^{31}$,

in which R^{31} is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)alkyl, optionally substituted lower alkoxy, optionally substituted phenyl or pyridinyl,

R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

R and R′ are each



in which R^4 is hydrogen, halogen, hydroxy, lower alkyl, optionally substituted lower alkoxy, trihalo(lower)alkyl, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, and n is an integer from 1 to 3,

provided R^4 may be different from each other when n is 2 or 3; and

R^5 is hydrogen, halogen, lower alkyl, lower alkylthio, lower alkanoylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl,

$-O-R^{51}$,

in which R^{51} is hydrogen, optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or

in which R^{52} is hydrogen or lower alkyl;

R^{53} is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group,

R^{52} and R^{53} may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

or a salt thereof.

(5) The aminopyrimidine compound of (4) above wherein

R^1 is hydrogen, methyl, ethyl, propyl, isopropyl, hydroxyisopropyl, methoxyisopropyl or benzyl;

R^2 is hydrogen, methyl, acetyl, benzoyl, toluoyl, methoxybenzoyl, trifluoromethylbenzoyl, fluorobenzoyl or chlorobenzoyl;

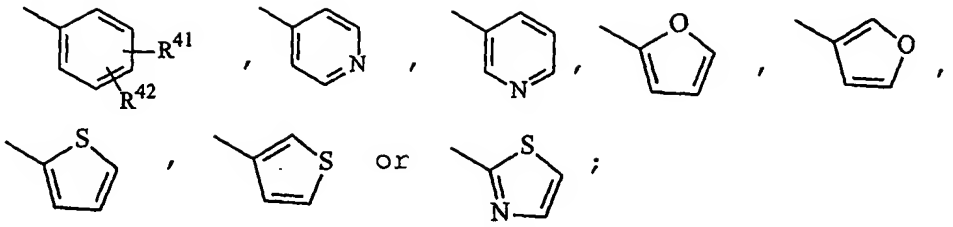
R^3 is hydrogen, methyl, phenyl, pyridinylmethyl or

$-CO-R^{31}$,

in which R^{31} is methyl, propyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, methoxy, methoxymethyl, trichloroethoxy, phenyl, tolyl, methoxyphenyl, trifluoromethylphenyl, fluorophenyl, chlorophenyl or pyridinyl, and

R^2 and R^3 may be combined together with N atom to which they are attached to form morpholino;

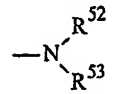
R and R′ are each



in which R^{41} and R^{42} are each independently hydrogen, fluoro, bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy, fluoropropoxy, dimethylaminoethoxy, morpholinylethoxy, methylthio, methylsulfinyl or methylsulfonyl; and

R^5 is hydrogen, fluoro, methyl, methylthio, acetylthio, phenylthio, methylsulfinyl, methylsulfonyl, $-O-R^{51}$,

in which R^{51} is hydrogen, methyl, ethyl, propyl, isopropyl, allyl, propynyl, cyclobutyl, cyclohexyl, hydroxyethyl, methoxyethyl, carboxymethyl, aminoethyl, dimethylaminoethyl, fluoroethyl, carbamoylmethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, cyclopropylcarbamoylmethyl, methoxycarbonylmethyl, tert-butoxycarbonylmethyl, acetylmethyl, benzoylmethyl, phenyl, benzyl, pyridinylmethyl, pyridinylethyl, tetrahydro-2H-pyranyl or 1,3(2H)-dioxoisoindolinylethyl, or



in which R^{52} is hydrogen or methyl,

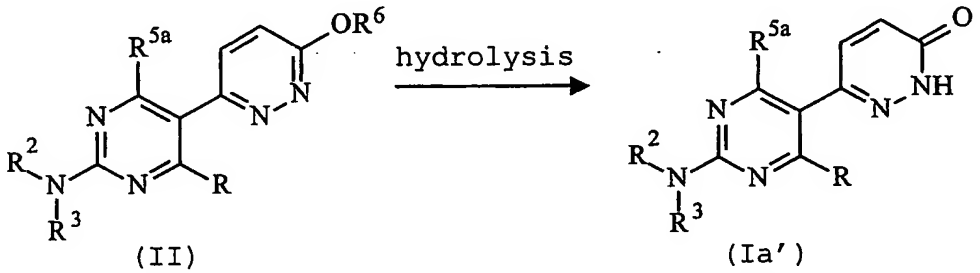
R^{53} is hydrogen, methyl, ethyl, propyl, isopropyl, tert-butyl, allyl, cyclopropyl, hydroxyethyl, methoxyethyl, aminoethyl, dimethylaminoethyl, carbamoylmethyl, amidino, phenyl, benzyl, pyridinyl, pyridinylmethyl, furylmethyl or dimethylthiazolyl,

R^{52} and R^{53} may be combined together with N atom to which they are attached to form pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl or benzimidazolyl,

or a salt thereof.

The object compound (I) and a salt thereof of the present invention can be prepared by the following processes.

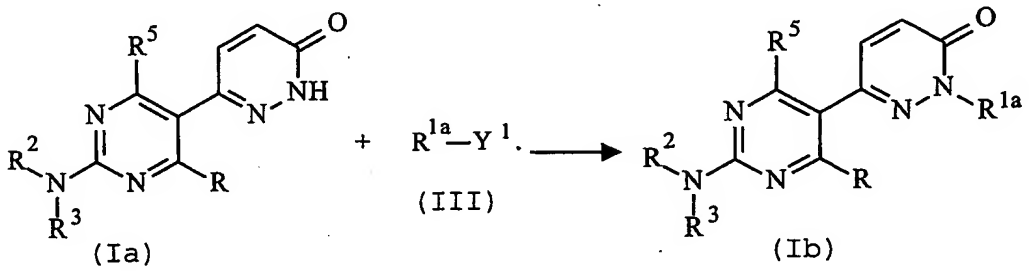
Process 1



(II)
or a salt thereof

(Ia')
or a salt thereof

Process 2

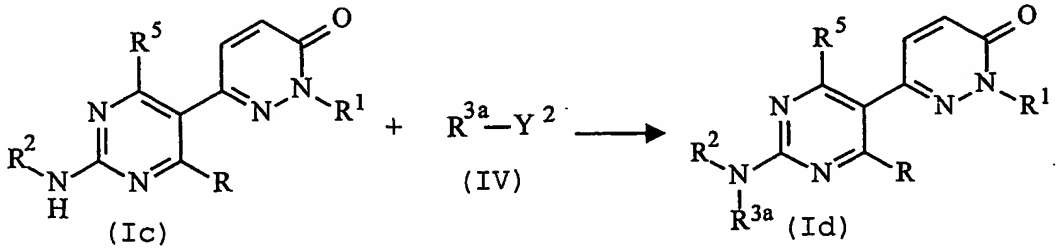


(Ia)
or a salt thereof

(III)

(Ib)
or a salt thereof

Process 3

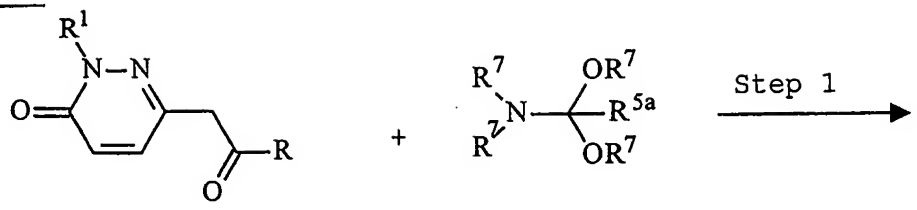


(Ic)
or a salt thereof

(IV)

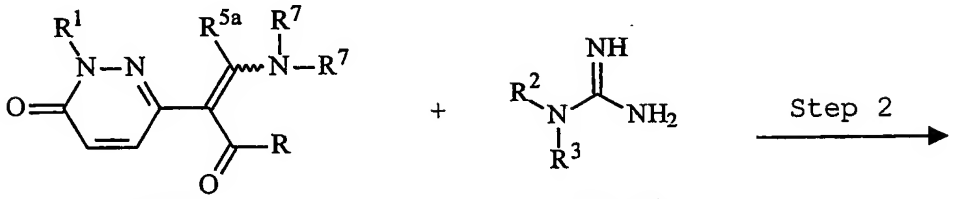
(Id)
or a salt thereof

Process 4



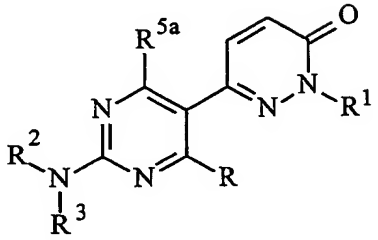
(V) (VI)

or a salt thereof or a salt thereof



(VII) (VIII)

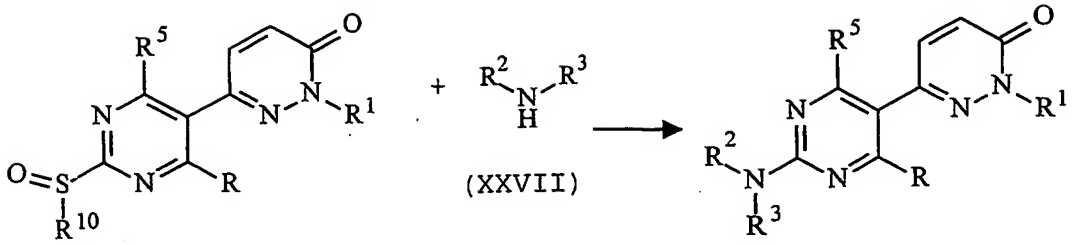
or a salt thereof or a salt thereof



(Ie)

or a salt thereof

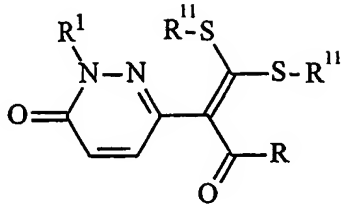
Process 5



(XXVI) (XXVII) (I)

or a salt thereof or a salt thereof

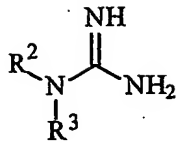
Process 6



(XXXII)

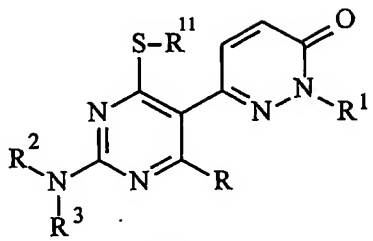
or a salt thereof

+



(VIII)

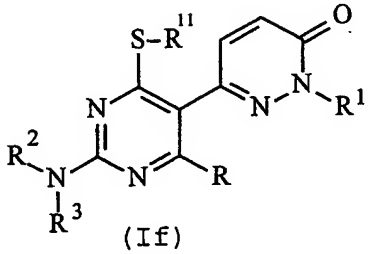
or a salt thereof



(If)

or a salt thereof

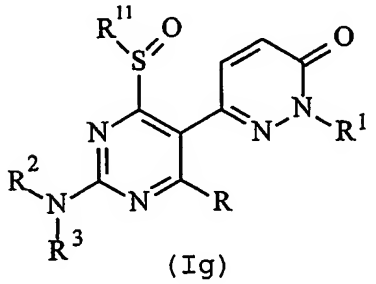
Process 7



(If)

or a salt thereof

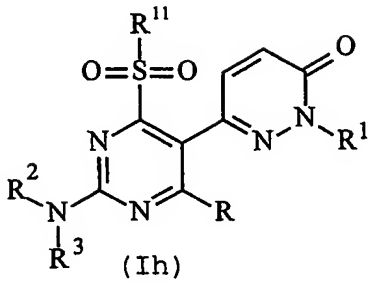
oxidation



(Ig)

or a salt thereof

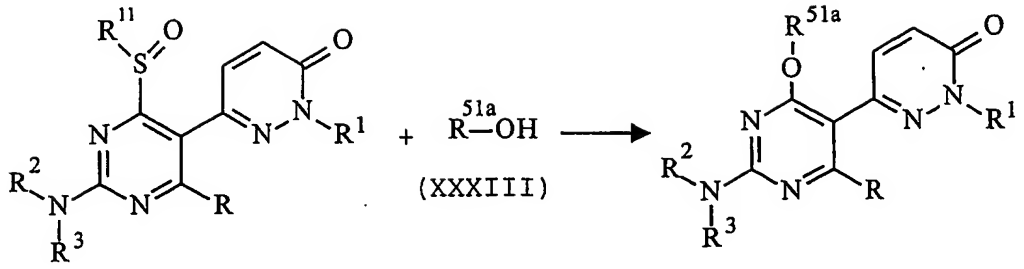
+



(Ih)

or a salt thereof

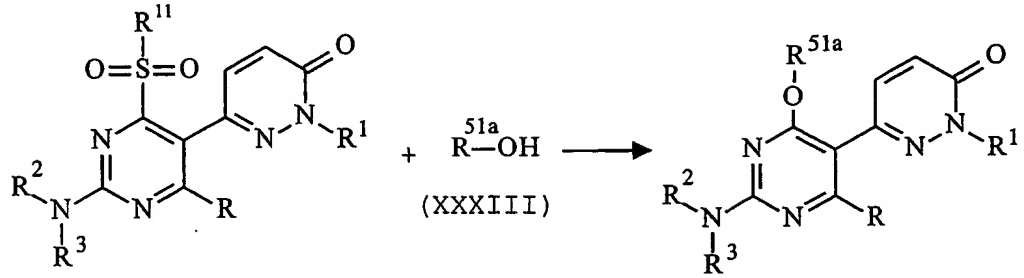
Process 8



(Ig) (XXXIII) (Ii)

or a salt thereof or a salt thereof

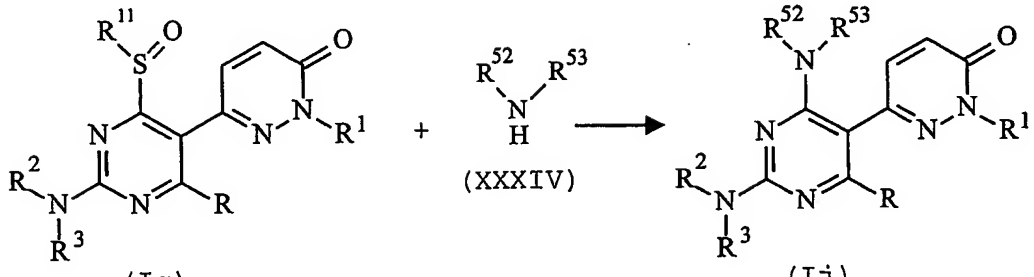
Process 9



(Ih) (XXXIII) (Ii)

or a salt thereof or a salt thereof

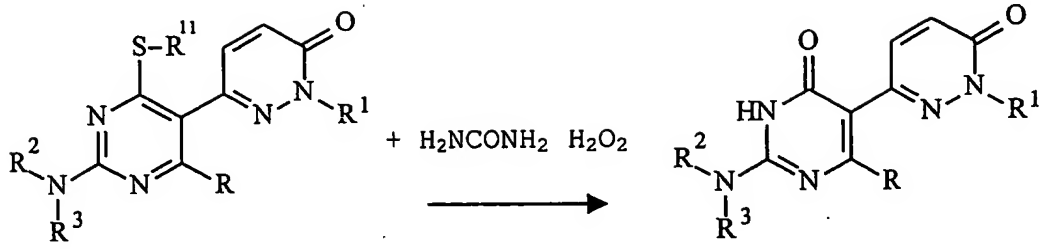
Process 10



(Ig) (XXXIV) (Ij)

or a salt thereof or a salt thereof

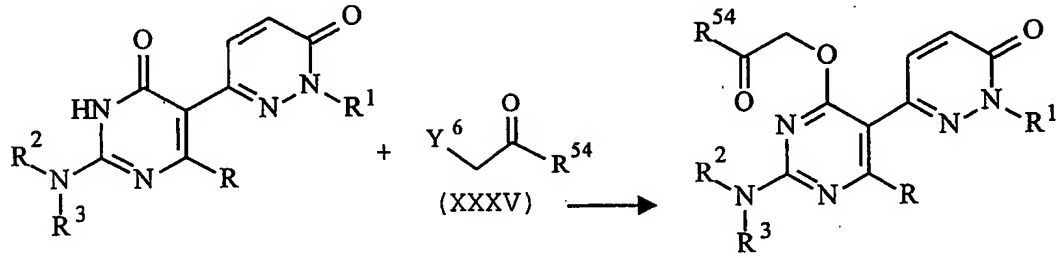
Process 11



(If)
or a salt thereof

(Ik)
or a salt thereof

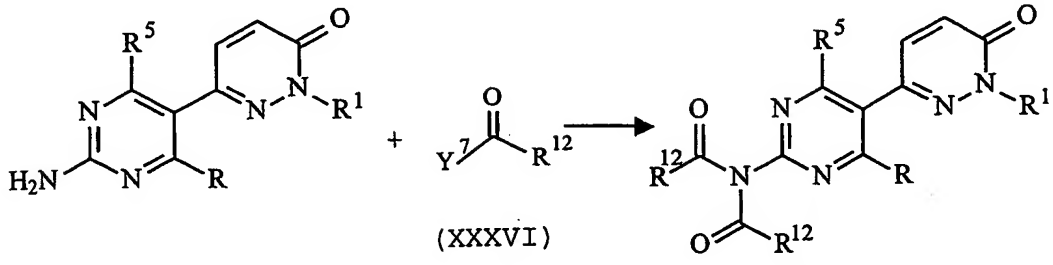
Process 12



(Ik)
or a salt thereof

(Il)
or a salt thereof

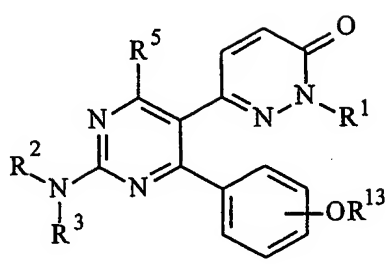
Process 13



(Im)
or a salt thereof

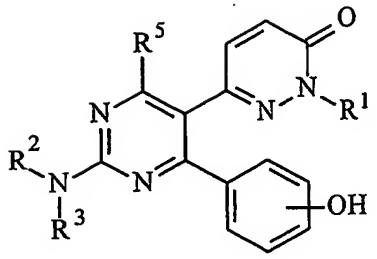
(In)
or a salt thereof

Process 14



(Io)

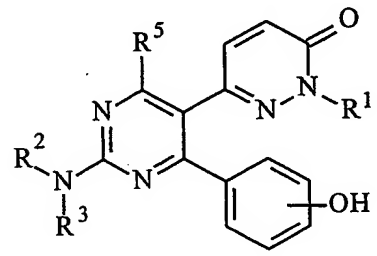
or a salt thereof



(Ip)

or a salt thereof

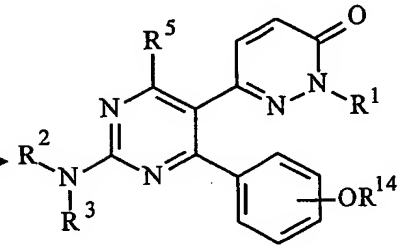
Process 15



(Ip)

or a salt thereof

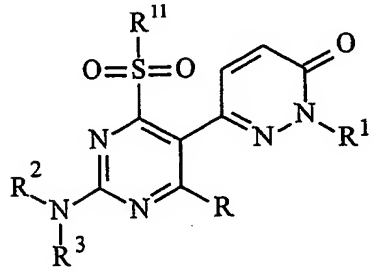
+ Y^8-R^{14} (XXXVII)



(Iq)

or a salt thereof

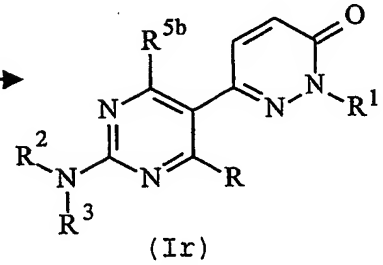
Process 16



(Ih)

or a salt thereof

+ Y^9-M-R^{5b} (XXXVIII)



(Ir)

or a salt thereof

wherein

R is optionally substituted aryl or heterocyclic group;

R^1 is hydrogen, optionally substituted lower alkyl, cyclo(lower)alkyl which may be interrupted by an oxygen atom or aryl(lower)alkyl;

R^{1a} is optionally substituted lower alkyl, cyclo(lower)alkyl which may be interrupted by an oxygen atom or aryl(lower)alkyl;

R^2 and R^3 are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

R^{3a} is lower alkyl, acyl, aryl or heterocyclic(lower)alkyl;

R^5 is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl;

R^{5a} is hydrogen, lower alkyl, optionally substituted hydroxy or optionally substituted amino;

R^{5b} is lower alkyl;

R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group,

R^{52} is hydrogen or lower alkyl;

R^{53} is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group, R^{52} and R^{53} may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

R^{54} is lower alkyl, cyclo(lower)alkyl, lower alkoxy or aryl;

R^6, R^7, R^{10}, R^{11} and R^{13} are each lower alkyl;

R^{12} is optionally substituted aryl or lower alkoxy;

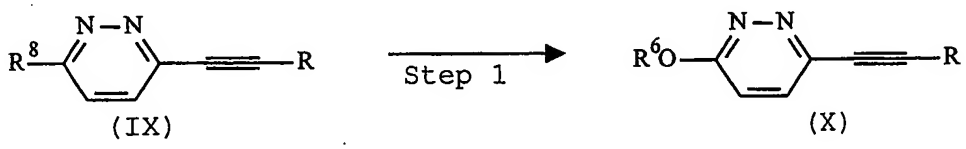
R^{14} is optionally substituted lower alkyl;

M is metal; and

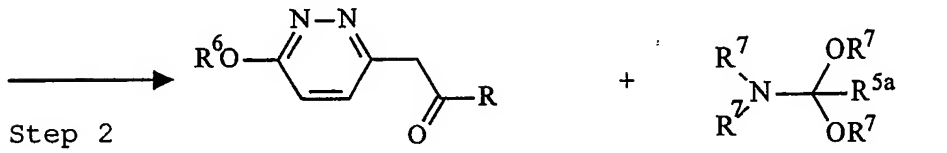
Y^1, Y^2, Y^6, Y^7, Y^8 and Y^9 are each a leaving group.

The starting compound(II) or a salt thereof is novel and can be prepared, for example, by the following reaction schemes.

Process A

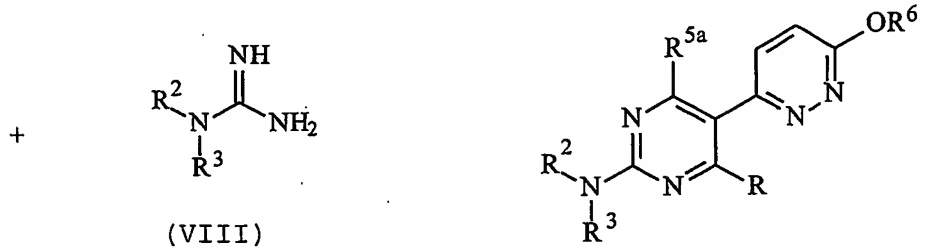


or a salt thereof or a salt thereof



or a salt thereof or a salt thereof

Step 3



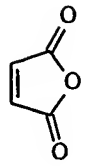
or a salt thereof

Step 4

or a salt thereof

wherein R, R^2, R^3, R^{5a}, R^6 and R^7 are as defined above, and R^8 is arylsulfonyl which may have one or more suitable substituent(s);

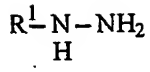
Process B



(XII)

or a salt thereof

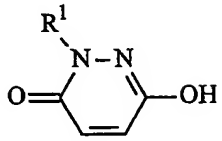
+



(XIII)

or a salt thereof

Step 1



(XIV)

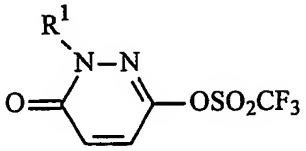
or a salt thereof

+ Tf_2O

(XV)

or a salt thereof

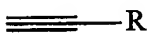
Step 2



(XVI)

or a salt thereof

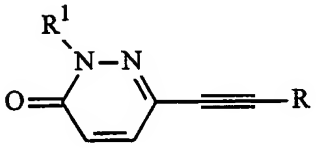
+



(XVII)

or a salt thereof

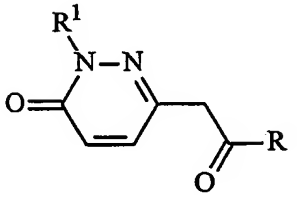
Step 3



(XVIII)

or a salt thereof

Step 4



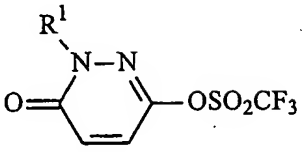
(V)

or a salt thereof

wherein R and R^1 are as defined above, and

Tf_2O is trifluoromethanesulfonic anhydride.

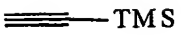
Process C



(XVI)

or a salt thereof

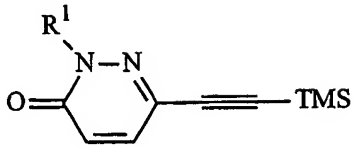
+



(XIX)

or a salt thereof

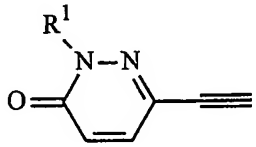
Step 1



(XX)

or a salt thereof

Step 2



+

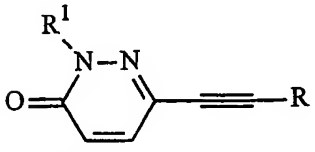
(XXI)

or a salt thereof

(XXII)

or a salt thereof

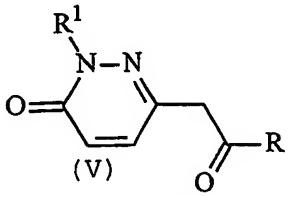
Step 3



(XVIII)

or a salt thereof

Step 4



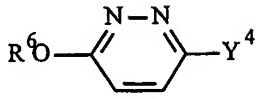
(V)

or a salt thereof

wherein R and R^1 are as defined above,

Y^3 is a leaving group, and TMS is trimethylsilyl.

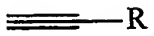
Process D



(XXIII)

or a salt thereof

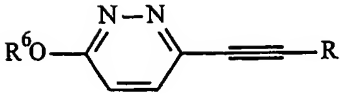
+



(XVII)

or a salt thereof

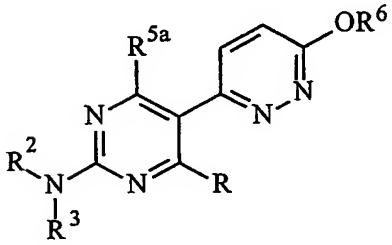
Step 1



(X)

or a salt thereof

Steps 2 to 4



(IIa)

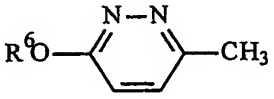
or a salt thereof

wherein R, R^2, R^3, R^{5a} and R^6 are as defined above,

Y^4 is a leaving group, and

Steps 2 to 4 in Process D are as same as those of Process A.

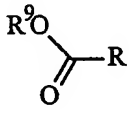
Process E



(XXIV)

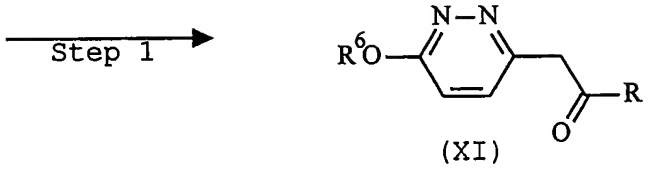
or a salt thereof

+



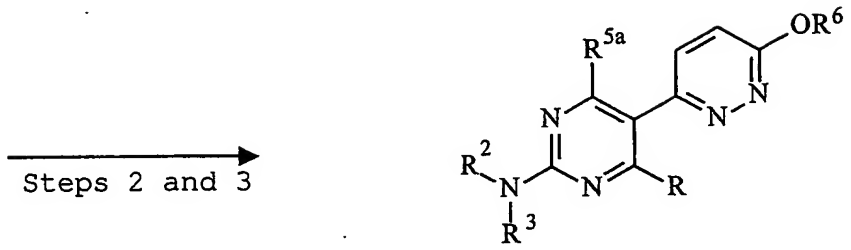
(XXV)

or a salt thereof



(XI)

or a salt thereof



(II)

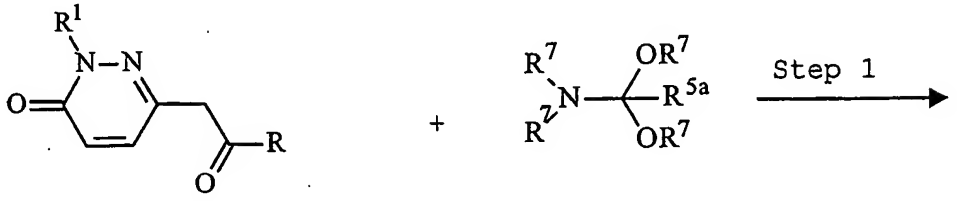
or a salt thereof

wherein R, R^2, R^3, R^{5a} and R^6 are as defined above,

R^9 is lower alkyl, and

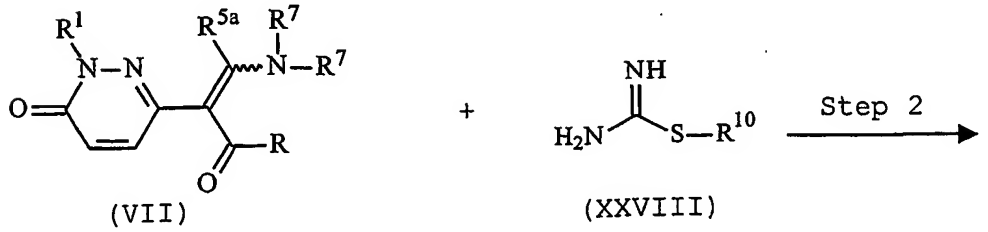
Steps 2 and 3 in Process E are as same as Steps 3 and 4 of Process A respectively.

Process F



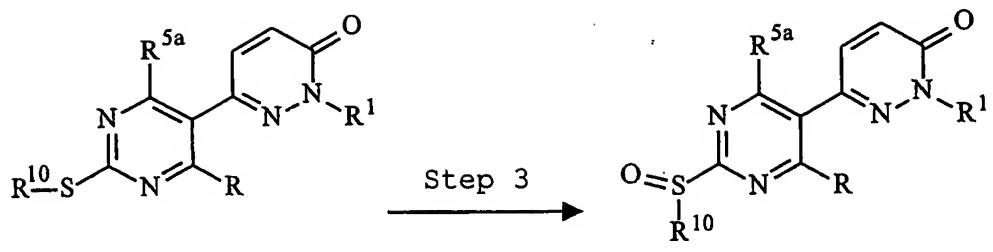
(V) (VI)

or a salt thereof or a salt thereof



(VII) (XXVIII)

or a salt thereof or a salt thereof

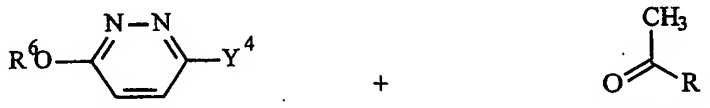


(XXIX)
or a salt thereof

(XXVI)
or a salt thereof

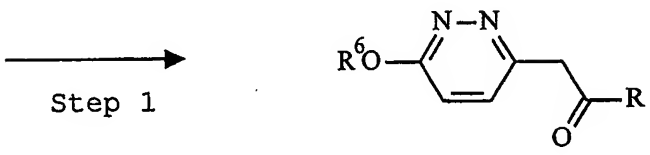
wherein R, R^1, R^{5a}, R^7 and R^{10} are as defined above, and Step 1 in Process F is as same as Step 1 of Process 4.

Process G

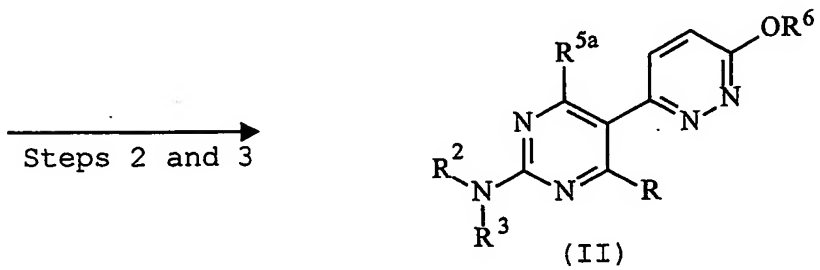


(XXIII)
or a salt thereof

(XXX)
or a salt thereof



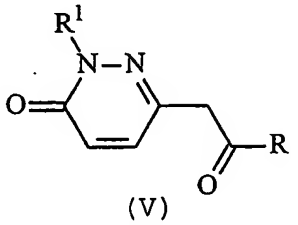
(XI)
or a salt thereof



(II)
or a salt thereof

wherein R, R^2, R^3, R^{5a}, R^6 and Y^4 are as defined above, and Steps 2 and 3 in Process G are as same as Steps 3 and 4 of Process A respectively.

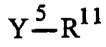
Process H



(V)

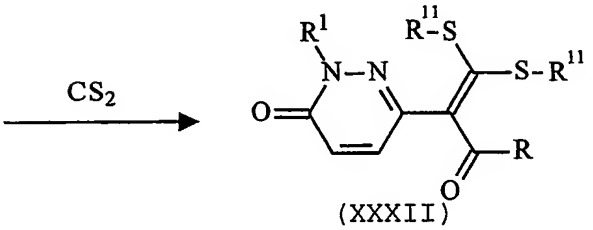
or a salt thereof

+



(XXXI)

or a salt thereof



(XXXII)

or a salt thereof

wherein R, R^1 and R^{11} are as defined above, and Y^5 is a leaving group.

In addition to the processes as mentioned above, the object compound (I) and a salt thereof can be prepared, for example, according to the procedures as illustrated in Examples in the present specification or in a manner similar thereto.

The starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto.

The object compound (I) and a salt thereof can be prepared according to the methods as shown in Preparations or Examples, or in a manner similar thereto.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, one isomer can be converted to another according to a conventional method in this field of the art.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

Suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof and which appear in the above and following description in the present specification are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which the preferred

one may be methyl, ethyl, propyl, isopropyl, isobutyl or tert-butyl.

Suitable "lower alkenyl" may include straight or branched ones such as vinyl, 1-propenyl, allyl, butenyl, pentenyl, hexenyl, or the like, in which the preferred one may be allyl.

Suitable "lower alkynyl" may include straight or branched ones such as ethynyl, propynyl, butynyl, or the like, in which the preferred one may be propynyl.

Suitable "lower alkoxy" may include straight or branched ones such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy, hexyloxy or the like.

Suitable "cyclo(lower)alkyl" may be cyclo(C3-C8)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like, in which the preferred one may be cyclopropyl, cyclobutyl or cyclohexyl.

Said "cyclo(lower)alkyl" may be interrupted by an oxygen atom, in which the preferred one may be saturated 3-8-membered heteromonocyclic group containing an oxygen atom such as tetrahydrofuranyl or tetrahydropyranyl.

Suitable "acyl" may include "optionally substituted carbonyl" such as carboxy, optionally substituted lower alkanoyl, optionally substituted lower alkoxycarbonyl, lower cycloalkanoyl, optionally substituted benzoyl, pyridinylcarbonyl or optionally substituted carbamoyl, or the like.

Suitable examples of aforesaid "lower alkanoyl" may include formyl, acetyl, propionyl, isopropionyl, butyryl, isobutyryl, tert-butyryl, valeryl, isovaleryl, pivaloyl, hexanoyl or the like, in which the preferred one may be (C1-C4)alkanoyl and the more preferred one may be acetyl propionyl, isopropionyl, butyryl, isobutyryl, tert-butyryl,.

Suitable substituent of aforesaid "substituted lower

alkanoyl" may include lower alkoxy (e.g. methoxy etc.), or the like.

Suitable examples of aforesaid "lower cycloalkanoyl" may be cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, in which the preferred one is cyclopropanoyl, cyclohexanoyl.

Suitable examples of aforesaid "optionally substituted lower alkoxycarbonyl" may be methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, trichloroethoxycarbonyl, or the like.

Suitable examples of aforesaid "optionally substituted benzoyl" may include benzoyl, halobenzoyl (e.g. fluorobenzoyl, chlorobenzoyl, etc.), lower alkyl benzoyl (e.g. toluoyl, etc.), lower alkoxybenzoyl (e.g. methoxybenzoyl, etc.), trihalo(lower)alkyl benzoyl (e.g. trifluoromethoxybenzoyl, etc.), or the like.

Suitable examples of aforesaid "optionally substituted carbamoyl" may include carbamoyl or N-substituted carbamoyl such as N-(lower)alkylcarbamoyl, N-cyclo(lower)alkylcarbamoyl, N,N-di(lower)alkylcarbamoyl, or the like, in which the preferred examples of "optionally substituted carbamoyl" may be carbamoyl, methylcarbamoyl, dimethylcarbamoyl, cyclopropylcarbamoyl, or the like.

Suitable "aryl" may include phenyl, naphthyl, indenyl, anthryl, or the like, in which the preferred one may be (C6-C10) aryl, and the more preferred one may be phenyl.

Suitable "heterocyclic group" may be saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from among oxygen, sulfur and nitrogen, and may be optionally substituted with lower alkyl such as methyl.

Preferable examples of "heterocyclic group" are described in the following.

3- through 8-membered unsaturated heteromonocyclic groups

containing 1 through 4 nitrogen atom(s), such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl (also referred to as pyridyl), and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g. 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 through 4 nitrogen atom(s), such as pyrrolidinyl, imidazolidinyl, piperidyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated condensed heterocyclic groups containing 1 through 5 nitrogen atom(s), such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g. tetrazolo[1,5-b]pyridazinyl etc.), dihydrotriazolopyridazinyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 or 2 oxygen atoms and 1 through 3 nitrogen atom(s), such as oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 or 2 oxygen atom(s) and 1 through 3 nitrogen atoms, such as morpholinyl, oxazolidinyl (e.g. 1,3-oxazolidinyl etc.), etc.;

unsaturated condensed heterocyclic groups containing 1 or 2 oxygen atom(s) and 1 through 3 nitrogen atom(s), such as benzoxazolyl, benzoxadiazolyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 or 2 sulfur atom(s) and 1 through 3 nitrogen atom(s), such as 1,3-thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl

(e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 or 2 sulfur atom(s) and 1 through 3 nitrogen atom(s), such as thiazolidinyl etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 sulfur atom, such as thienyl etc.;

unsaturated condensed heterocyclic groups containing 1 or 2 sulfur atoms and 1 through 3 nitrogen atom(s), such as benzothiazolyl, benzothiadiazolyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 or 2 oxygen atom(s), such as furyl, pyranyl, dioxolyl, etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 or 2 oxygen atom(s), such as oxolanyl, tetrahydropyranyl (e.g. tetrahydro-2H-pyran-2-yl etc.), dioxolanyl, etc.; and

unsaturated condensed heterocyclic groups containing 1 or 2 oxygen atom(s), such as isobenzofuranyl, chromenyl (e.g. 2H-chromen-3-yl etc.), dihydrochromenyl (e.g. 3,4-dihydro-2H-chromen-4-yl etc.), etc.

The particularly preferred example of said "heterocyclic group" may include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, furyl, thienyl, thiazolyl, dimethylthiazolyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, methylpiperazinyl, tetrahydro-2H-pyranyl, benzimidazolyl, 1,3(2H)-dioxoisoindolinyl.

Suitable "N-containing heterocyclic group" may be aforesaid "heterocyclic group", in which said group contains at least one N atom in its ring members, and may be optionally substituted with lower alkyl such as methyl.

Preferable examples of "N-containing heterocyclic group"

may include pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl, benzimidazolyl, etc.

Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which the preferred one may be fluoro or bromo.

Suitable "trihalo(lower)alkyl" may include trifluoromethyl, trichloromethyl and tribromomethyl, in which more preferred one is trifluoromethyl.

Suitable "metal" may include magnesium, zinc, or the like.

Suitable "a leaving group" may include halogen as mentioned above, hydroxy, acyloxy such as alkanoyloxy (e.g. acetoxy, propionyloxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), or the like.

Suitable "arylsulfonyl" may include phenylsulfonyl, tolylsulfonyl, naphthylsulfonyl and the like, and said "arylsulfonyl" may have one or more (preferably 1 to 3) suitable substituent(s) such as aforesaid lower alkoxy, aforesaid halogen, or the like.

Suitable examples of the substituent of "optionally substituted hydroxy" may include optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group or the like.

Preferable examples of the substituent of "optionally substituted hydroxy" may include hydroxy, methoxy, ethoxy, propoxy, isopropoxy, allyloxy, propynyloxy, cyclobutoxy, cyclohexyloxy, hydroxyethoxy, methoxyethoxy, carboxymethoxy, aminoethoxy, dimethylaminoethoxy, fluoroethoxy, carbamoylmethoxy, methylcarbamoylmethoxy, dimethylcarbamoylmethoxy, cyclopropylcarbamoylmethoxy, methoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, acetylmethoxy, benzoylmethoxy, phenoxy, benzyloxy, pyridinylmethoxy, pyridinylethoxy, tetrahydro-2H-pyranyloxy or 1,3(2H)-dioxoisoindolinylethoxy.

Suitable examples of the substituent of "optionally

substituted amino which may form N-containing heterocyclic group" may include optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl, heterocyclic group or the like, and they may be combined together with N atom to which they are attached to form N-containing heterocyclic group.

Preferable examples of "optionally substituted amino which may form N-containing heterocyclic group" may include amino, methylamino, ethylamino, propylamino, isopropylamino, tert-butylamino, allylamino, cyclopropylamino, hydroxyethylamino, methoxyethylamino, aminoethylamino, dimethylaminoethylamino, carbamoylmethylamino, amidinoamino, anilino, benzylamino, pyridinylamino, pyridinylmethylamino, furylmethylamino, dimethylthiazolylamino, dimethylamino, benzyl(methyl)amino, pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl or benzimidazolyl.

Suitable examples of the substituent of "optionally substituted lower alkyl" may include halo, trihalo, hydroxy, lower alkoxy, optionally substituted amino, acyl, aryl, heterocyclic group or the like.

Preferable examples of "optionally substituted lower alkyl" may include methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, fluoroethyl, trifluoromethyl, hydroxyethyl, hydroxyisopropyl, methoxyethyl, methoxyisopropyl, carboxymethyl, aminoethyl, dimethylaminoethyl, carbamoylmethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, cyclopropylcarbamoylmethyl, methoxycarbonylmethyl, tert-butoxycarbonylmethyl, acetylmethyl, benzoylmethyl, benzyl, pyridinylmethyl, pyridinylethyl, furylmethyl or 1,3(2H)-dioxoisoindolinylethyl.

Suitable examples of the substituent of "optionally

substituted lower alkoxy" may include halo, trihalo, lower alkoxy, optionally substituted amino, or heterocyclic group or the like.

Preferable examples of "optionally substituted lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy, hexyloxy fluoroethoxy, fluoropropoxy, trichloroethoxy, methoxyethoxy, dimethylaminoethoxy or morpholinylethoxy.

Suitable examples of the substituent of "optionally substituted aryl", "optionally substituted phenyl" or "optionally substituted benzoyl" may include halo, hydroxy, lower alkyl, optionally substituted lower alkoxy, trihalo(lower)alkyl, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, or the like.

Preferable examples of "optionally substituted aryl" may include phenyl which may be substituted with fluoro, bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy, fluoropropoxy, dimethylaminoethoxy, morpholinylethoxy, methylthio, methylsulfinyl or methylsulfonyl.

Suitable examples of the substituent of "optionally substituted mercapto" may include lower alkyl, lower alkanoyl, aryl, or the like.

Preferable examples of "optionally substituted mercapto" may include methylthio, acetylthio or phenylthio.

The processes for preparing the object aminopyrimidine compound(I) are explained in detail in the following.

Process 1

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to hydrolysis.

Suitable salt of the compound (II) can be referred to an

acid addition salt as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamide (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid includes an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid such as BBr_3, BCl_3, BF_3, $AlCl_3$, $TiCl_4$ or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with the compound

(III) or a salt thereof.

Suitable salt of the compound (Ia) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (III) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (III) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride, etc.), organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y^1 is -OH, activation of OH with triphenylphosphine and the like may be necessary.

Process 3

The compound (Id) or a salt thereof can be prepared by reacting the compound (Ic) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salt of the compound (Ic) and (IV) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, pyridine or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (IV) is in liquid, it can also be used as a solvent.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y^2 is -OH, activation of OH with triphenylphosphine

and the like may be necessary.

Process 4

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (V) or a salt thereof to formation reaction of pyrimidine ring.

Suitable salt of the compound (V) and (VI) can be referred to the ones as exemplified for the compound (I).

Suitable salt of the compound (VIII) can be referred to an acid addition salt as exemplified for the compound (I), in which the preferred one is hydrochloride.

This reaction can be carried out by reacting the compound (V) or a salt thereof with the compound (VI) or a salt thereof (Step 1), and further reacting with the compound (VIII) or a salt thereof (Step 2).

The reactions may be carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction. These conventional solvents may also be used in a mixture with water. In case of Step 1, the compound VI can also be used as a single solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. MeONa, EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction

is usually carried out at ambient temperature, under warming or under heating.

Process 5

The compound (I) or a salt thereof can be prepared by reacting the compound (XXVI) or a salt thereof with the compound (XXVII) or a salt thereof.

Suitable salt of the compound (XXVI) and (XXVII) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The reaction can be carried out by the method disclosed in Example 17 mentioned later or the similar manner thereto.

Process 6

The compound (If) or a salt thereof can be prepared by reacting the compound (XXXII) or a salt thereof with the compound (VIII) or a salt thereof.

Suitable salt of the compound (XXXII) and (VIII) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such

as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The reaction can be carried out by the method disclosed in Example 78 mentioned later or the similar manner thereto.

Process 7

The compounds (Ig) and (Ih) or salts thereof can be prepared by oxidizing the compound (If) or a salt thereof.

The oxidation is carried out in the presence of an oxidizer such as 3-chloroperbenzoic acid.

Suitable salt of the compound (If) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The reaction can be carried out by the method disclosed in Example 79 mentioned later or the similar manner thereto.

Process 8

The compound (Ii) or a salt thereof can be prepared by reacting the compound (Ig) or a salt thereof with the compound (XXXIII) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction

temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed in Example 80, 81, 85 and 89 mentioned later or the similar manner thereto.

Process 9

The compound (Ii) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (XXXIII) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed in Example 91, 93, 94 and 95 mentioned later or the similar manner thereto.

Process 10

The compound (Ij) or a salt thereof can be prepared by reacting the compound (Ig) or a salt thereof with the compound (XXXIV) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed in Example 105, 114, 115, 118, 119, 120, 128, 130 and 133 mentioned later or the similar manner thereto.

Process 11

The compound (Ik) or a salt thereof can be prepared by reacting the compound (If) or a salt thereof with urea hydrogen peroxide addition compound.

This reaction can be carried out by the method disclosed in Example 140 mentioned later or the similar manner thereto.

Process 12

The compound (Il) or a salt thereof can be prepared by reacting the compound (Ik) or a salt thereof with the compound (XXXV) or a salt thereof.

Suitable salt of the compound (Ik) and (XXXV) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

This reaction can be carried out by the method disclosed in Example 159 mentioned later or the similar manner thereto.

Process 13

The compound (In) or a salt thereof can be prepared by reacting the compound (Im) or a salt thereof with the compound (XXXVI) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process 3, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 3.

The reaction is preferably conducted in the presence of N-ethyl-N,N-diisopropylamine.

The reaction can be carried out by the method disclosed in Example 178 mentioned later or the similar manner thereto.

Process 14

The compound (Ip) or a salt thereof can be prepared by subjecting the compound (Io) or a salt thereof to elimination reaction of alkyl group.

Suitable salts of the compound (Io) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide or carbonate or bicarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.),hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid includes an organic acid (e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid (e.g. aluminium chloride, boron tribromide, boron trichloride, titanium trichloride, tin tetrachloride, etc.) or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction of this process can be also carried out according to a conventional reduction method employed in this field of the art (e.g. chemical reduction, catalytic reduction, etc.).

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 15

The compound (Iq) or a salt thereof can be prepared by reacting the compound (Ip) or a salt thereof with the compound (XXXVII) or a salt thereof.

Suitable salt of the compound (Ip) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (XXXVII) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (XXXVII) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride, etc.), organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate,

potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y^8 is -OH, activation of OH with triphenylphosphine and the like may be necessary.

Process 16

The compound (Ir) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (XXXVIII) or a salt thereof.

This reaction can be carried out by the method disclosed in Example 253 mentioned later or the similar manner thereto.

Process A

The reactions of steps 1 and 2 can be respectively carried out by the methods disclosed in Preparations 1 and 2 mentioned later or the similar manners thereto.

The reactions of steps 3 and 4 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process B

The reactions of steps 1 to 4 can be respectively carried out by the methods disclosed in Preparations 6 to 9 mentioned later or the similar manners thereto.

Process C

The reactions of steps 1 to 4 can be respectively carried out by the methods disclosed in Preparations 10 to 12 and 9 mentioned later or the similar manners thereto.

Process D

The reaction of Step 1 can be carried out by the method disclosed in Preparation 13 mentioned later or the similar manners thereto.

The reaction of step 2 can be carried out by the method

disclosed in Preparation 2 mentioned later or the similar manners thereto.

The reactions of steps 3 and 4 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process E

The reaction of Step 1 can be carried out by the method disclosed in Preparation 15 mentioned later or the similar manners thereto.

The reactions of steps 2 and 3 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process F

The reaction of step 1 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

The reaction of Step 2 can be carried out by the method disclosed in Preparation 20 mentioned later or the similar manners thereto.

The oxidation reaction of step 3 can be carried out by the method disclosed in Preparation 21 mentioned later or the similar manners thereto.

Process G

The reaction of Step 1 can be carried out by the method disclosed in Preparation 43 mentioned later or the similar manners thereto.

The reactions of steps 2 and 3 can be carried out in the same manner as in the aforementioned Process 4, and therefore

the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process H

The compound (XXXII) or a salt thereof can be prepared by reacting the compound (V) or a salt thereof with the compound (XXXI) or a salt thereof.

This reaction can be carried out by the method disclosed in Preparation 77 mentioned later or the similar manners thereto.

The object compound (I) of the present invention is an adenosine antagonist and possesses the various pharmacological actions as stated before.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

[I] Test compound

6-(2-Amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (Example 1)

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-ethyl-3(2H)-pyridazinone (Example 4)

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]acetamide (Example 7)

2-Isopropyl-6-{4-phenyl-2-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-3(2H)-pyridazinone (Example 18)

6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (Example 47)

6-(2-Amino-4-fluoro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (Example 136)

6-{2-Amino-4-[4-(2-methoxyethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (Example 212)

[II] Test method

Test 1 : Adenosine antagonistic activity

The adenosine antagonistic activity [Ki(nM)] of the test compound was examined by radioligand binding techniques using 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3-^{3}H(N)] ([^{3}H]DPCPX, 4.5nM) for human A_1 receptor and [^{3}H]CGS 21680 (20nM) for human A_{2a} receptor.

Test 2 : Anticatalepsy activity in Mouse

The test compound (3.2mg/kg) was administered orally with ddY mice(n=7). Then, haloperidol (0.32mg/kg) was injected intraperitoneally 30 min. after the administration of the compound. Thirty min. after the injection, the cataleptic responses of mice were measured. The forelimbs of each mouse were placed on a 3 cm high, 3 mm wide horizontal bar, and the duration of cataleptic posture was measured for up to 30 sec.

[III] Test result

Test 1 : Adenosine antagonistic activity

Table 1

Test compound (Example No.)	Adenosine receptor binding (Ki:nM)	
	A_1	A_{2a}
1	11.35	3.85
4	3.14	4.35
7	6.47	2.09
18	10.78	7.38
47	7.74	1.38
136	1.75	1.41
212	2.36	1.70

Test 2 : Anticatalepsy activity in Mouse

Table 2

Test compound (Example No.)	Manifestation rate of catalepsy (number of mouse)
1	4/7
4	0/7
7	0/7
18	0/7
47	1/7
136	0/7
212	0/7

The aminopyrimidine compound (I) and a salt thereof of this invention are useful as adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and for the prevention and/or the treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, and

the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the aminopyrimidine compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where necessary. The aminopyrimidine compound (I) or a pharmaceutically acceptable salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral administration, or insufflation. While the dosage of therapeutically effective amount of the aminopyrimidine compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose

of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A suspension of 3-(phenylethynyl)-6-(phenylsulfonyl)-pyridazine (138.8 g) in MeOH (1.4 l) was cooled in an ice bath. 28% NaOMe in MeOH (92 g) was added dropwise to the mixture at 10°C over a period of 10 minutes and the mixture was stirred at 5-10°C for 1 hour and 15 minutes. After the solvent was removed under reduced pressure, the residue was partitioned between EtOAc(1000 ml) and water (500 ml). After an additional extraction with EtOAc (500 ml), the combined extracts were washed with brine (500 ml), dried over anhydrous $MgSO_4$, and concentrated to give crude material, which was then purified by silica gel column chromatography (n-Hexane:EtOAc, 2:1 v/v) to afford 3-methoxy-6-(phenylethynyl)pyridazine (68.8 g) as colorless crystals.

mp: 98-99°C

IR (Nujol): 2214, 1651 cm^{-1}

NMR (DMSO-d_6, δ): 4.10(3H, s), 7.30(1H, d, J=9.1Hz), 7.46-7.53(3H, m), 7.64-7.69(2H, m), 7.86(1H, d, J=9.1 Hz).

ESI/MS: 233 $[M+Na]^+$

Preparation 2

To a solution of 3-methoxy-6-(phenylethynyl)pyridazine (24.0 g) in AcOH (360 ml) was added dropwise conc. H_2SO_4 (120 ml) and the mixture was heated to reflux for 4.5 hours. AcOH was removed under reduced pressure and the residue was poured into ice (1 kg). Aqueous NaOH was added to the mixture to neutralize and extracted with EtOAc (x 3). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under

reduced pressure. The crude material was purified by column chromatography on silica-gel (n-Hexane-EtOAc, 1:1 v/v) to give 2-(6-methoxy-3- pyridazinyl)-1-phenylethanone (24.53 g) as yellow crystals.

mp: 103-104°C

IR (Nujol): 1678, 1652 cm^{-1}

NMR ($CDCl_3$, δ): 4.11 (3H, s), 4.61 (2H, s), 6.95 (1H, d, J = 9.1 Hz), 7.39-7.59 (4H, m), 8.07-8.12 (2H, m).

ESI/MS: 229 $[M+H]^+$

Preparation 3

A mixture of 2-(6-methoxy-3-pyridazinyl)-1-phenylethanone (1.50 g) and N,N-dimethylformamide dimethylacetal (1.57 g) was heated to reflux for 2.5 hours. The mixture was cooled to ambient temperature, washed with n-hexane (3 times) and dried to give an oil (1.91 g). The oil was dissolved in EtOH, and guanidine hydrochloride (1.26 g) and 28% NaOMe / in MeOH (2.60 g) was added to the mixture, which was then heated to reflux for 2.5 hours. The mixture was poured into ice/water and extracted with EtOAc (x 2). The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica-gel column chromatograpy ($CHCl_3$-MeOH, 50:1 v/v) to give 2-amino-5-(6-methoxy-3- pyridazinyl)-4-phenylpyrimidine (1.36 g) as colorless crystals.

IR (Nujol): 3325, 3192, 1653, 1562, 1538 cm^{-1}

NMR (DMSO-d_6, δ): 4.03(3H, s), 6.99-7.11(4H, m), 7.25-7.43(5H, m), 8.49(1H, s)

ESI/MS: 279 $[M+Na]^+$

Elemental Analysis for $C_{15}H_{13}N_5O$

Calcd.: C,64.51; H,4.69; N,25.08

Found : C,64.45; H,4.74; N,24.93

Preparation 4

5-(6-Methoxy-3-pyridazinyl)-N-methyl-4-phenyl-2-

pyrimidinamine was obtained from 2-(6-methoxy-3-pyridazinyl)-1- phenylethanone, N,N-dimethylformamide dimethylacetal and 1-methylguanidine hydrochloride according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ): 2.91(3H, d, J=4.8 Hz), 4.03(3H, s), 7.02(1H, d, J=9.2 Hz), 7.09(1H, d, J=9.2 Hz), 7.32-7.52(6H, m), 8.53(1H, brd. s)

ESI/MS: 316 $[M+Na]^+$

Preparation 5

5-(6-Methoxy-3-pyridazinyl)-N,N-dimethyl-4-phenyl-2-pyrimidinamine was obtained from 2-(6-methoxy-3-pyridazinyl)-1- phenylethanone, N,N-dimethylformamide dimethylacetal and 1,1-dimethylguanidine hydrochloride according to a similar manner to that of Preparation 3.

NMR (DMSO-d_6, δ): 3.24(6H, s), 4.03(3H, s), 7.03(1H, d, J=9.2 Hz), 7.10(1H, d, J=9.2 Hz), 7.31-7.41(5H, m), 8.59(1H, s).

ESI/MS: 330 $[M+Na]^+$

Preparation 6

To a solution of maleic anhydride (41.57 g) in glacial acetic acid (310 ml) was added 1-isopropylhydrazine (31.43 g) at ambient temperature. The mixture was heated under reflux for 5 hours and concentrated under reduced pressure to give a solid. The solid was triturated by isopropyl ether, collected by filtration, and recrystalized from a mixture of methanol and isopropyl ether to give 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (60.27 g).

mp: 162-164°C (methanol - isopropyl ether)

IR (KBr) : 1504 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.22(6H, d, J=6.66 Hz), 5.03(1H, 7-plet, J=6.65 Hz), 6.85(1H, d, J=9.62 Hz), 7.01(1H, d, J=9.62 Hz),

10.95(1H, br.s)
APCI/MS: 155 $[M+H]^+$
Elemental Analysis for $C_7H_{10}N_2O_2$
Calcd.: C,54.54; H,6.54; N,18.17
Found : C,54.72; H,6.61; N,18.13

Preparation 7

To a solution of 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (5.00 g) in pyridine (32 ml) was dropwise added tifluoromethanesulfonic anhydride (5.51 ml) under ice-cooling. The mixture was stirred under ice-cooling for one hour and at ambient temperature for 3 hours. Pyridine was removed under reduced pressure to give a residue. The residue was dissolved a mixture of ethyl acetate and water. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 8:2 v/v) to give 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethane- sulfonate as a solid (8.66 g).
mp: 45-46°C (n-hexane)
IR (KBr) : 1660, 1587 cm^{-1}
^1H NMR ($CDCl_3$, δ) : 1.34(6H, d, J=6.62 Hz), 5.23(1H, 7-plet, J=6.61 Hz), 7.04(1H, d, J=9.83 Hz), 7.16(1H, d, J=9.83 Hz)
APCI/MS: 287 $[M+H]^+$
Elemental Analysis for $C_8H_9F_3N_2O_4S$
Calcd.: C,33.57; H,3.17; N,9.79
Found : C,33.80; H,2.96; N,9.79

Preparation 8

In the presence of dichlorobis(triphenylphosphine)-palladium(II) (0.42 g) and copper(I) iodide (0.42 g), triethylamine (3.9 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethane- sulfonate (5.73 g), 1-ethynyl-4-fluorobenzene (3.65 g) in dioxane (60 ml) at 75-80°C

for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, water and chloroform were added to the reaction mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 7:3 v/v) to give 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)- pyridazinone as a solid (4.22 g).

mp: 105.5-106.5°C (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 5.33(1H, 7-plet, J=6.64 Hz), 6.87(1H, d, J=9.57 Hz), 7.01-7.14(2H, m), 7.28(1H, d, J=9.57 Hz), 7.51-7.61(2H, m)

APCI/MS: 257 $[M+H]^+$, 215

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd.: C,70.30; H,5.11; N,10.93

Found : C,70.33; H,5.34; N,11.05

Preparation 9

To a mixture of sulfuric acid (6 ml) and acetic acid (15 ml) was added 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone (3.00 g) and the mixture was heated at 100-105°C for 40 minutes. The solution was poured into a mixuture of ice (90 g) and sodium carbonate (25.4 g), extracted with ethyl acetate (24 ml x 2), dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 3:7 v/v) to give 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone as a solid (451 mg).

mp: 67-68°C (n-hexane)

IR (KBr) : 1689, 1660, 1596 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.62 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.62 Hz), 6.89(1H, d, J=9.50 Hz), 7.11-7.23(3H, m),

8.04-8.13(2H, m)

APCI/MS: 275 $[M+H]^+$, 233

Elemental Analysis for $C_{15}H_{15}FN_2O_2$

Calcd.: C,65.68; H,5.51; N,10.21

Found : C,65.72; H,5.65; N,10.21

Preparation 10

In the presence of dichlorobis(triphenylphosphine)-palladium(II) (1.47 g) and copper(I) iodide (1.47 g), triethylamine (14.67 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo- 1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (20.10 g), (trimethylsilyl)acetylene (24.81 ml) in tetrahydrofuran (300 ml) under ice-cooling for 2 hours. The mixture was stirred at ambient temperature for 3 hours. The reaction mixture was poured into a mixture of water and ethyl acetate. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 9:1 v/v) to give 2-isopropyl-6-[(trimethylsilyl)ethynyl]-3(2H)- pyridazinone as a solid (16.10 g).

mp: 61-62.5°C (n-hexane)

IR (KBr) : 2160, 1664, 1587 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 0.27(9H, s), 1.37(6H, d, J=6.64 Hz), 5.29(1H, 7-plet, J=6.64 Hz), 6.81(1H, d, J=9.54 Hz), 7.21(1H, d, J=9.54 Hz), 7.51-7.61(2H, m)

ESI/MS: 491 $[2M+Na]^+$, 257 $[M+Na]^+$, 235 $[M+H]^+$

Elemental Analysis for $C_{12}H_{18}N_2OSi$

Calcd.: C,61.50; H,7.74; N,11.95

Found : C,61.25; H,7.82; N,12.00

Preparation 11

To a solution of 2-isopropyl-6-[(trimethylsilyl)ethynyl]-3(2H)-pyridazinone and benzyltriethylammonium chloride (0.52

g) in a mixture of tetrahydrofuran (45 ml) and acetonitrile (45 ml) was added dropwise 12 N aqueous sodium hydroxide (60 ml) under ice-cooling. After stirring for 30 minutes, the mixture was acidified with concentrated hydrochloric acid under ice-cooling, extracted with chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 8:2 v/v) to give 6-ethynyl-2-isopropyl-3(2H)- pyridazinone as a solid(10.42 g).

mp: 103-104°C (acetone - n-hexane)

IR (KBr) : 3194, 2108, 1655, 1587 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.64 Hz), 3.19(1H, s), 5.31(1H, 7-plet, J=6.64 Hz), 6.85(1H, d, J=9.52 Hz), 7.22(1H, d, J=9.52 Hz)

ESI/MS: 185 $[M+Na]^+$, 163 $[M+H]^+$

Elemental Analysis for $C_9H_{10}N_2O$

Calcd.: C,66.65; H,6.21; N,17.27

Found : C,66.92; H,6.28; N,17.36

Preparation 12

In the presence of dichlorobis(triphenylphosphine)-palladium(II) (0.42 g) and copper(I) iodide (0.42 g), triethylamine (3.9 ml) was added dropwise to a mixture of 6-ethynyl-2-isopropyl- 3(2H)-pyridazinone (3.25 g), 1-fluoro-4-iodobenzene(6.67 g) in dioxane (60 ml) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, a mixture of water and ethyl acetate was added to the reaction mixture. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 7:3 v/v) to give 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)- pyridazinone as a solid (3.81 g).

mp: 105.5-106.5°C (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 5.33(1H, 7-plet, J=6.64 Hz), 6.87(1H, d, J=9.57 Hz), 7.01-7.14(2H, m), 7.28(1H, d, J=9.57 Hz), 7.51-7.61(2H, m)

APCI/MS: 257 $[M+H]^+$, 215

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd.: C,70.30; H,5.11; N,10.93

Found : C,70.33; H,5.34; N,11.05

Preparation 13

To a mixture of 3-methoxy-6-iodopyridazine (30.0 g), 2-bromo-1-ethynylbenzene (34.5 g), dichlorobis(triphenylphosphine)palladium (II) (892 mg) and copper (I) iodide (242 mg) in DMF (150 ml) was added triethylamine (23.0 ml) at ambient temperature under N_2 atmosphere and the resultant mixture was allowed to stir at the same temperature for 13 hours. The reaction mixture was poured into water and extracted with ethyl acetate (x2). The combined extracts were washed with brine and water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2, n-Hexane-EtOAc, 10:1) to afford 3-[(2-bromophenyl)ethynyl]-6-methoxypyridazine.

mp: 99-100°C

IR (Nujol): 1699, 1651, 1558, 1540 cm^{-1}

NMR($CDCl_3$, δ): 4.18(3H, s), 6.97(1H, d, J=9.2 Hz), 7.24-7.37(2H, m), 7.56-7.67(3H, m)

ESI/MS: 311, 313 $[M+Na]^+$, APCI/MS: 289, 291 $[M+H]^+$

Preparation 14

1-(2-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was obtained from 3-[(2-bromophenyl)ethynyl]-6-methoxypyridazine according to a similar manner to that of Preparation 2.

IR (Neat): 2956, 2925, 1733, 1699, 1651 cm^{-1}

ESI/MS: 380, 382 $[M+Na]^+$

Preparation 15

To a solution of 3-methoxy-6-methylpyridazine (371 mg) and ethyl 2-bromobenzoate (753 mg) in THF (4 ml) was added dropwise 1M lithium bis(trimethylsilyl)amide in THF (5.98 ml) at 5°C over a period of 20 minutes under N_2 atmosphere and the resulting solution was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice/water and pH was adjusted to neutral with 1N HCl, and the mixture was extracted with EtOAc (x2). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 935 mg of yellow oil. The crude material was purified by silica-gel column chromatography (n-Hexane-EtOAc, 10:3) to afford 1-(2-bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone as yellow oil.

Preparation 16

4-(Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was obtained from 1-(2-bromophenyl)-2-(6-methoxy-3- pyridazinyl)ethanone according to a similar manner to that of Preparation 3.

mp: 180-181°C (EtOH)

IR (Nujol): 1649, 1637, 1576, 1560, 1538 cm^{-1}

NMR (DMSO-d_6, δ): 3.98(3H, s), 7.02(1H, d, J=9.1 Hz), 7.08(1H, d, J=9.1 Hz), 7.16(2H, brd. s), 7.30-7.45(3H, m), 7.58(1H, d, J=7.9 Hz), 8.65(1H, s)

ESI/MS: 380, 382 $[M+Na]^+$

Preparation 17

In the presence of dichlorobis(triphenylphosphine)palladium (II) (0.49 g) and copper(I) iodide (0.133 g), a solution of triethylamine (11.7 ml) in dioxane (10 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl-

trifluoromethanesulfonate (20.00 g) and ethynylbenzene (8.56 g) in dioxane (70 ml) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, water and chloroform were added to the reaction mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 85 : 15 v/v) to give 2-isopropyl-6-(phenylethynyl)- 3(2H)-pyridazinone as a solid (16.17 g).

mp: 75.5-77°C (heptane)

IR (KBr) : 2218, 1669, 1583 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.65 Hz), 5.33(1H, 7-plet, J=6.65 Hz), 6.87(1H, d, J=9.57 Hz), 7.26-7.42(4H, m), 7.52-7.60(2H, m)

ESI/MS: 499 $[2M+Na]^+$, 261 $[M+Na]^+$, 239 $[M+H]^+$

Elemental Analysis for $C_{15}H_{14}N_2O$

Calcd.: C,75.61; H,5.92; N,11.76

Found : C,75.79; H,5.88; N,11.74

Preparation 18

To a mixture of sulfuric acid (1 ml) and acetic acid (3 ml) was added 2-isopropyl-6-(phenylethynyl)-3(2H)-pyridazinone (479 mg) and the mixture was heated at 100-105°C for 2 hours. The solution was poured into water (80 ml), extracted with ethyl acetate (30 ml x 3), dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 25 : 75 v/v) to give 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone as a solid (451 mg).

mp: 50-53°C (diisopropyl ether - hexane)

IR (KBr): 1687, 1660, 1595 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.66 Hz), 4.32(2H, s), 5.29(1H,

7-plet, J=6.66 Hz), 6.88(1H, d, J=9.50 Hz), 7.18(1H, d, J=9.50 Hz), 7.45-7.62(3H, m), 8.01-8.07(2H, m)

ESI/MS: 535 $[2M+Na]^+$, 279 $[M+Na]^+$, 257 $[M+H]^+$

Elemental Analysis for $C_{15}H_{16}N_2O_2$

Calcd.: C,70.29; H,6.29; N,10.93

Found : C,69.17; H,6.32; N,10.74

Preparation 19

To a mixture of 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (500 mg) and N,N-dimethylformamide dimethyl acetal (0.518 ml) was heated at 100-105°C for one hour. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (chloroform) to give 6-[1-benzoyl-2-(dimethylamino)ethenyl]-2-isopropyl-3(2H)-pyridazinone as a solid (604 mg).

mp: 103-104.5°C (diisopropyl ether)

IR (KBr): 1647, 1628, 1583, 1554 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.64 Hz), 2.89(6H, s), 5.33(1H, 7-plet, J=6.64 Hz), 6.75(1H, d, J=9.43 Hz), 7.11(1H, d, J=9.43 Hz), 7.26-7.48(6H, m)

ESI/MS: 645 $[2M+Na]^+$, 334 $[M+Na]^+$, 312 $[M+H]^+$

Elemental Analysis for $C_{18}H_{21}N_3O_2 \cdot 0.1H_2O$

Calcd.: C,69.03; H,6.82; N,13.42

Found : C,69.08; H,6.75; N,13.34

Preparation 20

Under ice-cooling, potassium t-butoxide (1.75 g) was added to a suspension of 6-[1-benzoyl-2-(dimethylamino)ethenyl]-2-isopropyl-3(2H)-pyridazinone (1.21 g) and S-methylthiouronium sulfate (2.17 g) in methanol (15 ml). The mixture was stirred for one hour under ice-cooling and at ambient temperature for 30 hours. After removal of methanol under reduced pressure, A mixture of chloroform and water was added to a reaction mixture.

An organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 70 : 30 v/v) to give 2-isopropyl-6-[2-(methylthio)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (943 mg).

mp: 143-144.5°C (ethanol - diisopropyl ether)

IR (KBr): 1655, 1593 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.33(6H, d, J=6.62 Hz), 2.66(3H, s), 5.33(1H, 7-plet, J=6.62 Hz), 6.71(1H, d, J=9.70 Hz), 6.75(1H, d, J=9.70 Hz), 7.34-7.52(5H, m), 8.73(1H, s)

ESI/MS: 699 $[2M+Na]^+$, 361 $[M+Na]^+$, 399 $[M+H]^+$

Elemental Analysis for $C_{18}H_{18}N_4OS$

Calcd.: C,63.88; H,5.36; N,16.56

Found : C,64.00; H,5.24; N,16.57

Preparation 21

A mixture of 2-isopropyl-6-[2-(methylthio)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone (990 mg) and urea-hydrogen peroxide complex (550 mg) in acetic acid (0.99 ml) was stirred at ambient temperature for 40 hours. After addition of chloroform, the mixture was washed with water, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol- chloroform 3:97 v/v) to give 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (516 mg).

mp: 178-179°C (acetone - diisopropyl ether)

IR (KBr): 1666, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.35(6H, d, J=6.66 Hz), 3.06(3H, s), 5.35(1H, 7-plet, J=6.66 Hz), 6.77(1H, d, J=9.56 Hz), 6.84(1H, d, J=9.56 Hz), 7.38-7.57(5H, m), 9.06(1H, s)

ESI/MS: 731 $[2M+Na]^+$, 377 $[M+Na]^+$

Elemental Analysis for $C_{18}H_{18}N_4O_2S$
Calcd.: C,61.00; H,5.12; N,15.81
Found : C,61.12; H,5.16; N,15.56

Preparation 22

6-[(2-Fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was obtained from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-fluoro-2-iodobenzene according to a similar manner to that of Preparation 12.
mp: 84.5-86°C (diisopropyl ether - hexane)
IR (KBr): 2224, 1660, 1644, 1583 cm^{-1}
^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.62 Hz), 5.34(1H, 7-plet, J=6.62 Hz), 6.88(1H, d, J=9.52 Hz), 7.12-7.20(2H, m), 7.32(1H, d, J=9.52 Hz), 7.33-7.41(1H, m), 7.52-7.60(1H, m)
ESI/MS: 535 $[2M+Na]^+$, 279 $[M+Na]^+$, 257 $[M+H]^+$
Elemental Analysis for $C_{15}H_{13}FN_2O$
Calcd.: C,70.30; H,5.11; N,10.93
Found : C,70.38; H,5.14; N,10.95

Preparation 23

6-[2-(2-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[(2-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.
IR (Neat): 1685, 1664, 1593 cm^{-1}
^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.65 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.65 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m), 8.02-8.04(1H, m)
ESI/MS: 571 $[2M+Na]^+$, 297 $[M+Na]^+$, 275 $[M+H]^+$

Preparation 24

6-[2-(Dimethylamino)-1-(2-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(2-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar

manner to that of Example 13(1).

mp: 79.5-81.5°C (chloroform - hexane)

IR (KBr): 1668, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.28(6H, d, J=6.62 Hz), 2.89(6H, br.s), 5.29(1H, 7-plet, J=6.62 Hz), 6.77(1H, d, J=9.46 Hz), 6.95-7.39(6H, m)

ESI/MS: 681 $[2M+Na]^+$, 352 $[M+Na]^+$, 330 $[M+H]^+$

Elemental Analysis for $C_{18}H_{20}FN_3O_2$

Calcd.: C,65.64; H,6.12; N,12.76

Found : C,65.49; H,6.36; N,12.80

Preparation 25

6-[(3-Fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-fluoro-3-iodobenzene according to a similar manner to that of Preparation 12.

mp: 95.5-96.5°C (acetone - hexane)

IR (KBr): 2220, 1660, 1606, 1585 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.62 Hz), 5.34(1H, 7-plet, J=6.62 Hz), 6.88(1H, d, J=9.52 Hz), 7.12-7.20(2H, m), 7.32(1H, d, J=9.52 Hz), 7.33-7.41(1H, m), 7.52-7.60(1H, m)

ESI/MS: 535 $[2M+Na]^+$, 279 $[M+Na]^+$, 257 $[M+H]^+$

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd.: C,70.30; H,5.11; N,10.93

Found : C,70.22; H,5.16; N,10.94

Preparation 26

6-[2-(3-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[(3-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 80-81°C (diisopropyl ether - hexane)

IR (KBr): 1680, 1658, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.60 Hz), 4.29(2H, s), 5.29(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.48 Hz), 7.18(1H, d, J=9.48

Hz), 7.26-7.33(1H, m), 7.43-7.53(1H, m), 7.70-7.77(1H, m), 7.80-7.86(1H, m)

ESI/MS: 274 $[2M+Na]^+$, 297 $[M+Na]^+$, 275 $[M+H]^+$

Elemental Analysis for $C_{15}H_{15}FN_2O_2$

Calcd.: C,65.68; H,5.51; N,10.21

Found : C,65.73; H,5.61; N,10.24

Preparation 27

6-[2-(Dimethylamino)-1-(3-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(3-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1651, 1574, 1558 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.63 Hz), 2.89(6H, br.s), 5.33(1H, 7-plet, J=6.63 Hz), 6.75(1H, d, J=9.46 Hz), 7.07-7.36(5H, m), 7.45(1H, s)

ESI/MS: 681 $[2M+Na]^+$, 352 $[M+Na]^+$, 330 $[M+H]^+$

Preparation 28

6-[(2-Chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-chloro-2-iodobenzene according to a similar manner to that of Preparation 12.

mp: 95.5-96°C (acetone - hexane)

IR (KBr): 1660, 1585 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.63 Hz), 5.34(1H, 7-plet, J=6.63 Hz), 6.88(1H, d, J=9.56 Hz), 7.24-7.37(3H, m), 7.43-7.47(1H, m), 7.58-7.64(1H, m)

ESI/MS: 569 and 567 $[2M+Na]^+$, 297 and 295 $[M+Na]^+$

Elemental Analysis for $C_{15}H_{13}ClN_2O$

Calcd.: C,66.06; H,4.80; N,10.27

Found : C,66.17; H,4.80; N,10.26

Preparation 29

6-[2-(2-Chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-

pyridazinone was prepared from 6-[(2-chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 81.5-82°C (diisopropyl ether - hexane)

IR (KBr): 1685, 1657, 1589 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.27(6H, d, J=6.66 Hz), 4.03(2H, s), 5.26(1H, 7-plet, J=6.66 Hz), 6.89(1H, d, J=9.48 Hz), 7.19(1H, d, J=9.48 Hz), 7.29-7.46(3H, m), 7.55-7.60(1H, m)

ESI/MS: 605 and 603 $[2M+Na]^+$, 315 and 313 $[M+Na]^+$, 293 and 291 $[M+H]^+$

Elemental Analysis for $C_{15}H_{15}ClN_2O_2$

Calcd.: C,61.94; H,5.20; N,9.63

Found : C,61.54; H,5.35; N,9.54

Preparation 30

6-[2-(Dimethylamino)-1-(2-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(2-chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1655, 1576 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.64 Hz), 2.89(6H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.76(1H, d, J=9.44 Hz), 7.21-7.36(6H, m)

ESI/MS: 681 $[2M+Na]^+$, 352 $[M+Na]^+$, 330 $[M+H]^+$

Preparation 31

6-[(3-Chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate and 1-chloro-3-ethynylbenzene according to a similar manner to that of Preparation 8.

mp: 94-95°C (heptane)

IR (KBr): 1664, 1589 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.40(6H, d, J=6.65 Hz), 5.33(1H, 7-plet,

J=6.65 Hz), 6.88(1H, d, J=9.54 Hz), 7.25-7.48(4H, m), 7.55-7.58(1H, m)

ESI/MS: 569 and 567 $[2M+Na]^+$, 297 and 295 $[M+Na]^+$, 275 and 273 $[M+H]^+$

Elemental Analysis for $C_{15}H_{13}ClN_2O$

Calcd.: C,66.06; H,4.80; N,10.27

Found : C,66.10; H,4.83; N,10.27

Preparation 32

6-[2-(3-Chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[(3-chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 85-86°C (diisopropyl ether - hexane)

IR (KBr): 1676, 1658, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.65 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.65 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m), 8.02-8.04(1H, m)

ESI/MS: 605 and 603 $[2M+Na]^+$, 315 and 313 $[M+Na]^+$, 293 and 291 $[M+H]^+$

Elemental Analysis for $C_{15}H_{15}ClN_2O_2$

Calcd.: C,61.97; H,5.20; N,9.63

Found : C,62.10; H,5.25; N,9.68

Preparation 33

6-[2-(Dimethylamino)-1-(3-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(3-chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1657, 1579, 1556 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.66 Hz), 2.90(6H, br.s), 5.34(1H, 7-plet, J=6.66 Hz), 6.76(1H, d, J=9.40 Hz), 7.08(1H, d, J=9.40 Hz), 7.21-7.38(4H, m), 7.44(1H, s)

ESI/MS: 348 and 346 $[M+H]^+$

Elemental Analysis for $C_{18}H_{20}ClN_3O_2 \cdot 0.4H_2O$

Calcd.: C,61.24; H,5.94; N,11.90

Found : C,61.20; H,6.06; N,11.78

Preparation 34

2-Isopropyl-6-{[2-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-2-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

mp: 88.5-90°C (hexane)

IR (KBr): 1664, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.60 Hz), 5.34(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.54 Hz), 7.30(1H, d, J=9.54 Hz), 7.45-7.60(2H, m), 7.69-7.76(2H, m)

ESI/MS: 635 $[2M+Na]^+$, 329 $[M+Na]^+$, 307 $[M+H]^+$

Elemental Analysis for $C_{16}H_{13}F_3N_2O$

Calcd.: C,62.74; H,4.28; N,9.15

Found : C,62.82; H,4.36; N,9.14

Preparation 35

2-Isopropyl-6-{2-oxo-2-[2-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{[2-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 91-92.5°C (diisopropyl ether - hexane)

IR (KBr): 1709, 1654, 1586 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.29(6H, d, J=6.68 Hz), 4.18(2H, s), 5.28(1H, 7-plet, J=6.68 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.50-7.79(4H, m)

ESI/MS: 671 $[2M+Na]^+$, 347 $[M+Na]^+$, 325 $[M+H]^+$

Elemental Analysis for $C_{16}H_{15}F_3N_2O_2$

Calcd.: C,59.26; H,4.66; N,8.64

Found : C,59.39; H,4.69; N,8.63

Preparation 36

6-{2-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[2-(trifluoromethyl)phenyl]-ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (KBr): 1654, 1587 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.33(6H, d, J=6.65 Hz), 2.84(6H, br.s), 5.33(1H, 7-plet, J=6.65 Hz), 6.79(1H, d, J=8.96 Hz), 7.21-7.70(6H, m)

ESI/MS: 781 $[2M+Na]^+$, 402 $[M+Na]^+$, 380 $[M+H]^+$

Preparation 37

2-Isopropyl-6-{[3-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-3-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

mp: 102.5-104°C (hexane)

IR (KBr): 1662, 1589 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.60 Hz), 5.34(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.54 Hz), 7.30(1H, d, J=9.54 Hz), 7.47-7.56(1H, m), 7.65(1H, d, J=7.86 Hz), 7.74(1H, d, J=7.86 Hz), 7.84(1H, s).

ESI/MS: 635 $[2M+Na]^+$, 329 $[M+Na]^+$

Elemental Analysis for $C_{16}H_{13}F_3N_2O$

Calcd.: C,62.74; H,4.28; N,9.15

Found : C,62.72; H,4.29; N,9.19

Preparation 38

2-Isopropyl-6-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{[3-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

IR (Neat): 1695, 1657, 1591 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.31(6H, d, J=6.62 Hz), 4.34(2H, s), 5.28(1H,

7-plet, J=6.62 Hz), 6.90(1H, d, J=9.50 Hz), 7.18(1H, d, J=9.50 Hz), 7.66(1H, t, J=7.80 Hz), 7.87(1H, d, J=7.90 Hz), 8.23(1H, d, J=7.90 Hz), 8.30(1H, s)

ESI/MS: 671 $[2M+Na]^+$, 347 $[M+Na]^+$, 325 $[M+H]^+$

Elemental Analysis for $C_{16}H_{15}F_3N_2O_2$

Calcd.: C,59.26; H,4.66; N,8.64

Found : C,58.99; H,4.75; N,8.57

Preparation 39

6-{3-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1651, 1558 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.33(6H, d, J=6.66Hz), 2.92(6H, br.s), 5.32(1H, , J=6.66 Hz), 6.76(1H, d, J=9.40 Hz), 7.07(1H, d, J=9.40 Hz), 7.41-7.68(5H, m)

ESI/MS: 781 $[2M+Na]^+$, 402 $[M+Na]^+$, 380 $[M+H]^+$

Preparation 40

2-Isopropyl-6-{[4-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-4-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

mp: 48-50°C (hexane)

IR (KBr) : 1662, 1585 cm-1

^1H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.60 Hz), 5.34(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.54 Hz), 7.30(1H, d, J=9.54 Hz), 7.64(1H, d, J=8.88 Hz), 7.68(1H, d, J=8.88 Hz)

ESI/MS: 635 $[2M+Na]^+$, 329 $[M+Na]^+$, 307 $[M+H]^+$

Elemental Analysis for $C_{16}H_{13}F_3N_2O$

Calcd.: C,62.74; H,4.28; N,9.15

Found : C,62.91; H,4.47; N,9.06

Preparation 41

2-Isopropyl-6-{2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{[4-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 99-101°C (hexane)

IR (KBr): 1686, 1660, 1595 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.31(6H, d, J=6.62 Hz), 4.34(2H, s), 5.28(1H, 7-plet, J=6.62 Hz), 6.90(1H, d, J=9.50 Hz), 7.18(1H, d, J=9.50 Hz), 7.77(2H, d, J=8.15 Hz), 8.15(2H, d, J=8.15 Hz)

ESI/MS: 671 $[2M+Na]^+$, 347 $[M+Na]^+$, 325 $[M+H]^+$

Elemental Analysis for $C_{16}H_{15}F_3N_2O_2$

Calcd.: C,59.26; H,4.66; N,8.64

Found : C,59.45; H,4.66; N,8.70

Preparation 42

6-{4-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1651, 1558 cm^{-1}

^1H NMR ($CDCl_3$, δ): 1.29(6H, d, J=6.64 Hz), 2.91(6H, br.s), 5.32(1H, 7-plet, J=6.64 Hz), 6.79(1H, d, J=9.48 Hz), 7.12(1H, d, J=9.48 Hz), 7.41(1H, s), 7.51-7.63(4H, m)

ESI/MS: 781 $[2M+Na]^+$, 402 $[M+Na]^+$, 380 $[M+H]^+$

Preparation 43

4'-Methoxyacetophenone (1.5 g) was dissolved in tetrahydrofuran (25 ml). To the solution was added sodium tert-butoxide (575 mg) at 25°C. To the solution was added tris(dibenzylideneacetone)-dipalladium(0) (229 mg) and racemic-2,2'- bis(diphenyl phosphino)-1,1'-binaphthyl (311 mg), followed by 3-methoxy-6-chloropyridazine (720 mg). The mixture was heated at 75°C and stirred for 3 hours.

The reaction mixture was portioned to dichloromethane and 0.1N-hydrochloric acid. The organic layer was separated. The aqeous layer was extracted with dichlorometane. The combined organic layer was dried over magnesium sulfate. The solution was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (ethyl acetate: hexane=1:1) to give 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone (671 mg).

IR (KBr): 3490, 1668, 1469, 1263 cm^{-1}

NMR (DMSO-d_6, δ): 3.86(3H, s), 4.00(3H, s), 4.63(2H, s), 7.06(2H, d, J=9.8 Hz), 7.20(1H, d, J=9.2 Hz), 7.56(1H, d, J=9.2 Hz), 8.05(1H, d, J=9.8 Hz)

ESI/MS: 259 $[M+H]^+$, 281 $[M+Na]^+$

Preparation 44

1-(3-Fluorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-fuoroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3488, 1670, 1469, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 3.99(3H, s), 4.72 (2H, s), 7.19-7.94 (6H, m)

ESI/MS: 247 $[M+H]^+$, 269 $[M+Na]^+$

Preparation 45

1-(3-Fluoro-4-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)-ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-fluoro-4'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1685, 1444, 1230 cm^{-1}

NMR (DMSO-d_6, δ): 3.95(3H, s), 4.00(3H, s), 4.65(2H, s), 7.20(1H, d, J=9.0 Hz), 7.29-7.38(1H, m), 7.67(1H, d, J=9.0 Hz), 7.83-7.98(2H, m)

ESI/MS: 277 $[M+H]^+$, 299 $[M+Na]^+$

Preparation 46

1-(4-Chlorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 4'-chloroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 4.00(3H, s), 4.70(2H, s), 7.19-8.10(6H, m)

ESI/MS: 263 and 265 $[M+H]^+$, 285 and 287 $[M+Na]^+$

Preparation 47

2-(6-Methoxy-3-pyridazinyl)-1-(3-pyridinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3-acetylpyridine according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 4.00(3H, s), 4.76(2H, s), 7.15-9.24(6H, m)

ESI/MS: 230 $[M+H]^+$, 252 $[M+Na]^+$

Preparation 48

2-(6-Methoxy-3-pyridazinyl)-1-(4-pyridinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 4-acetylpyridine according to a similar manner to that of Preparation 43.

IR (KBr): 3490, 1665, 1465, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 4.01(3H, s), 4.75(2H, s), 7.14-7.39(2H, m), 7.58-7.93(2H, m), 8.67-8.86(2H, m)

ESI/MS: 230 $[M+H]^+$

Preparation 49

2-(6-Methoxy-3-pyridazinyl)-1-(1,3-thiazol-2-yl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2-acetylthiazole according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 3.93(3H, s), 4.76(2H, s), 7.20-8.50(4H, m)
ESI/MS: 236 $[M+H]^+$, 258 $[M+Na]^+$

Preparation 50

1-(2-Furyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2-acetylfuran according to a similar manner to that of Preparation 43.
IR (KBr): 3490, 1675, 1460, 1265 cm^{-1}
NMR ($CDCl_3$, δ): 4.11(3H, s), 4.45(2H, s), 6.55-6.58(1H, m), 6.96(1H, d, J=7.0 Hz), 7.26(1H, s), 7.37-7.39(1H, m), 7.44(1H, d, J=7.0 Hz), 7.63(1H, s)
ESI/MS: 219 $[M+H]^+$, 241 $[M+Na]^+$

Preparation 51

2-(6-Methoxy-3-pyridazinyl)-1-(4-methylphenyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 4'-methylacetophenone according to a similar manner to that of Preparation 43.
IR (KBr): 3490, 1675, 1460, 1265 cm^{-1}
NMR ($CDCl_3$, δ): 1.59(3H, s), 4.11(3H, s), 4.58(2H, s), 6.95(1H, d, J=9.0 Hz), 7.27(2H, d, J=6.6 Hz), 7.42(1H, d, J=9.0 Hz), 8.00(2H, d, J=6.6 Hz)
ESI/MS: 243 $[M+H]^+$, 265 $[M+Na]^+$

Preparation 52

1-(3,4-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl)-ethanone was prepared from 3-methoxy-6-chloropyridazine and 3',4'-difluoroacetophenone according to a similar manner to that of Preparation 43.
IR (KBr): 3485, 1685, 1600, 1465, 1260 cm^{-1}
NMR (DMSO-d_6, δ): 4.03(3H, s), 4.55(2H, s), 6.91(1H, d, J=9.6 Hz), 7.18(1H, d, J=9.6 Hz), 7.63-7.97 (3H, m)
ESI/MS: 265 $[M+H]^+$, 287 $[M+Na]^+$

Preparation 53

1-(3,4-Dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl)-

ethanone was prepared from 3-methoxy-6-chloropyridazine and 3',4'-dimethoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1680, 1595, 1455, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 3.93(3H, s), 3.95(3H, s), 4.11(3H, s), 4.56(2H, s), 6.89-6.97(2H, m), 7.43(1H, d, J=9.0 Hz), 7.59(1H, d, J=2.0 Hz), 7.82(1H, dd, J=8.2, 2 Hz)

ESI/MS: 289 $[M+H]^+$, 311 $[M+Na]^+$

Preparation 54

1-(3,4-Dichlorophenyl)-2-(6-methoxy-3-pyridazinyl)-ethanone was prepared from 3-methoxy-6-chloropyridazine and 3',4'-dichloroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1680, 1605, 1460, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 4.12(3H, s), 4.56(2H, s), 6.91-7.00(2H, m), 7.22-8.16(3H, m)

ESI/MS: 297, 299 and 301 $[M+H]^+$, 319, 321 and 323 $[M+Na]^+$

Preparation 55

2-(6-Methoxy-3-pyridazinyl)-1-(2-methylphenyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2'-methylacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3475, 1690, 1600, 1465, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 2.52(3H, s), 4.12(3H, s), 4.56(2H, s), 6.97(1H, d, J=9.0 Hz), 7.10-7.42(4H, m), 7.95(2H, d, J=6.6 Hz)

ESI/MS: 243 $[M+H]^+$, 265 $[M+Na]^+$

Preparation 56

1-(2-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3375, 1690, 1600, 1460, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 3.91(3H, s), 4.11(3H, s), 4.64(2H, s), 6.95(1H, d, J=9.0 Hz), 7.02(2H, m), 7.39(1H, d, J=9.0 Hz), 7.46-7.94(1H, m), 7.76-7.81(1H, m)

ESI/MS: 259 $[M+H]^+$, 281 $[M+Na]^+$

Preparation 57

2-(6-Methoxy-3-pyridazinyl)-1-(2-thienyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2-acetylthiophene according to a similar manner to that of Preparation 43.

IR (KBr): 3385, 1685, 1585, 1460, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 4.11(3H, s), 4.53(2H, s), 6.90(1H, d, J=9.0 Hz)7.13-7.17(1H, m), 7.68(1H, d, J=9.0 Hz), 7.69(1H, d, J=5.0 Hz), 7.97(1H, d, J=4.0 Hz)

ESI/MS: 235 $[M+H]^+$, 257 $[M+Na]^+$

Preparation 58

2-(6-Methoxy-3-pyridazinyl)-1-(3-methylphenyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-methylacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3475, 1690, 1600, 1465, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 2.42(3H, s), 4.12(3H, s), 4.61(2H, s), 6.96(1H, d, J=9.0 Hz), 7.10-7.45(4H, m), 7.90(2H, d, J=6.6 Hz)

ESI/MS: 243 $[M+H]^+$, 265 $[M+Na]^+$

Preparation 59

1-(3-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3470, 1688, 1605, 1470, 1260 cm^{-1}

NMR ($CDCl_3$, δ): 3.89(3H, s), 4.21(3H, s), 4.61(2H, s), 6.96(1H, d, J=9.0 Hz), 7.02(2H, m), 7.42(1H, d, J=9.0 Hz), 7.46-7.94(1H, m), 7.76-7.81(1H, m)

ESI/MS: 259 $[M+H]^+$, 281 $[M+Na]^+$

Preparation 60

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone (516 mg) was dissolved in N,N-dimethyl formamide dimethylacetal (10 ml). The solution was heated at 90°C for 2 hours. The solution was cooled to ambient temperature. Evaporation of solvent in vacuo gave oily black residue. The residue was dissolved in ethanol (10 ml). To the solution was added guanidine hydrochloride (384 mg) and 28% sodium methylate in methanol solution (0.77 ml). The reaction mixture was heated at 80-90°C, and stirred for 2 hours. The mixture was cooled to ambient temperature ,and portioned to ethyl acetate and water. The organic layer was separated and washed with brine. The combined aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate. The solution was concentrated under reduced pressure to give oily residue. The above residue was purified by column chromatography on silica gel (chloroform : methanol = 20:1) to give 4-(4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine, which was crystallized from ethanol-water (1:2 30 ml) (509 mg).

IR (KBr): 3376, 1610, 1533, 1463, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 3.75(3H, s), 4.03(3H, s), 6.90(1H, d, J=10 Hz),6.99(2H, brs), 7.02-7.13(4H, m), 7.25(1H, d), 8.43(1H, s)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Preparation 61

4-(3-Fluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3-fuorophenyl)-2-(6-methoxy- 3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3322, 1654, 1575, 1444, 1297 cm^{-1}

NMR (DMSO-d_6, δ): 4.02(3H, s), 6.99-7.45(6H, m), 8.51(1H, s)

ESI/MS: 298 $[M+H]^+$, 320 $[M+Na]^+$

Preparation 62

4-(3-Fluoro-4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3-fuoro-4-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3330, 1660, 1575, 1440, 1280 cm^{-1}

NMR (DMSO-d_6, δ): 3.83(3H, s), 4.04(3H, s), 6.94(1H, dd, J=1.16, 8.6 Hz), 7.05-7.26(6H, m), 8.45(1H, s)

ESI/MS: 328 $[M+H]^+$, 350 $[M+Na]^+$

Preparation 63

4-(4-Chlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(4-chlorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3380, 1620, 1533, 1463, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 4.03(3H, s), 7.06-7.44(6H, m), 8.49(1H, s)

ESI/MS: 314 and 316 $[M+H]^+$, 336 and 338 $[M+Na]^+$

Preparation 64

5-(6-Methoxy-3-pyridazinyl)-4-(3-pyridinyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(3-pyridinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3530, 1680, 1575, 1450, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 4.02(3H, s), 7.11(1H, d, J=9.2 Hz), 7.16(2H, brs), 7.32(1H, d, J=9.2 Hz), 7.36-7.40(1H, m), 7.64-7.70(1H, m), 8.44-8.45(1H, m), 8.54(1H, s), 8.53-8.57(1H, m)

ESI/MS: 281 $[M+H]^+$, 303 $[M+Na]^+$

Preparation 65

5-(6-Methoxy-3-pyridazinyl)-4-(4-pyridinyl)-2-

pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1- (4-pyridinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3535, 1680, 1580, 1460, 1250 cm^{-1}

NMR (DMSO-d_6, δ): 4.01(3H, s), 7.12(1H, d, J=9.2 Hz), 7.21-7.25(4H, m), 7.32(1H, d, J=9.2 Hz), 8.55(1H, s), 8.53-8.57(2H, m)

ESI/MS: 281 $[M+H]^+$, 303 $[M+Na]^+$

Preparation 66

5-(6-Methoxy-3-pyridazinyl)-4-(1,3-thiazol-2-yl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1- (1,3-thiazol-2-yl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3540, 1620, 1580, 1455, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 4.06(3H, s), 7.13(1H, d, J=9.2 Hz), 7.21(2H, s), 7.60(1H, d, J=9.2 Hz), 7.77(1H, d, J=1.1 Hz), 7.90(1H, d, J=1.1 Hz), 8.43(1H, s)

ESI/MS: 287 $[M+H]^+$, 309 $[M+Na]^+$

Preparation 67

4-(2-Furyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3199, 1662, 1570, 1463, 1295 cm^{-1}

NMR (DMSO-d_6, δ): 4.05(3H, s), 6.55-6.58(1H, m), 6.77(1H, d, J=3.6 Hz),7.01(2H, s), 7.21(1H, d, J=9.2 Hz), 7.49(1H, d, J=9.2 Hz), 7.66-7.67(1H, m), 8.33(1H, s)

ESI/MS: 270 $[M+H]^+$, 292 $[M+Na]^+$

Preparation 68

5-(6-Methoxy-3-pyridazinyl)-4-(4-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(4-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3180, 1625, 1567, 1460, 1298 cm^{-1}

NMR (DMSO-d_6, δ): 2.29(3H, s), 4.03(sH, s), 7.00-7.21(8H, m), 8.45(1H, s)

ESI/MS: 316 $[M+Na]^+$

Preparation 69

4-(3,4-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-difluorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3178, 1654, 1575, 1465, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 4.03(3H, s), 7.06-7.47(7H, m), 8.51(1H, s)

ESI/MS: 316 $[M+H]^+$, 388 $[M+Na]^+$

Preparation 70

4-(3,4-Dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3174, 1644, 1587, 1465, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 3.59(3H, s), 3.74(3H, s), 4.03(3H, s), 6.74-7.14(7H, m), 8.43(1H, s)

ESI/MS: 340 $[M+H]^+$, 362 $[M+Na]^+$

Preparation 71

4-(3,4-Dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-dichlorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3318, 1629, 1583, 1461, 1294 cm^{-1}

NMR (DMSO-d_6, δ): 4.03(3H, s), 7.06-7.44(6H, m), 7.09(1H, d, J=9.0 Hz), 7.14(1H, d, J=8.2 Hz), 7.18(2H, s), 7.33(1H, d, J=9.0 Hz), 7.56(1H, d, J=8.2 Hz), 7.65(1H, s), 8.52(1H, s)

ESI/MS: 348, 350 and 352 $[M+H]^+$, 370, 372 and 374 $[M+Na]^+$

Preparation 72

5-(6-Methoxy-3-pyridazinyl)-4-(2-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(2-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3120, 1630, 1580, 1465, 1250 cm^{-1}

NMR (DMSO-d_6, δ): 1.98(3H, s), 3.99(3H, s), 6.85-7.31(6H, m), 7.06(2H, s), 8.60(1H, s)

ESI/MS: 294 $[M+H]^+$, 316 $[M+Na]^+$

Preparation 73

4-(2-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(2-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3127, 1634, 1580, 1455, 1267 cm^{-1}

NMR (DMSO-d_6, δ): 3.28(3H, s), 3.98(3H, s), 6.88(1H, d, J=8.6 Hz), 7.01(2H, brs), 7.02-7.05(3H, m), 7.34-7.42(2H, m)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Preparation 74

5-(6-Methoxy-3-pyridazinyl)-4-(2-thienyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(2-thienyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3124, 1637, 1575, 1458, 1285 cm^{-1}

NMR (DMSO-d_6, δ): 4.05(3H, s), 6.55-6.58(1H, m), 6.77(1H, d, J=3.6 Hz), 7.01(2H, s), 7.21(1H, d, J=9.2 Hz), 7.49(1H, d, J=9.2 Hz), 7.66-7.67(1H, m), 8.33(1H, s)

ESI/MS: 286 $[M+H]^+$, 308 $[M+Na]^+$

Preparation 75

5-(6-Methoxy-3-pyridazinyl)-4-(3-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(3-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3135, 1625, 1585, 1466, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 2.26(3H, s), 4.03(3H, s), 6.91-7.37(8H, m), 8.48(1H, s)

ESI/MS: 294 $[M+H]^+$, 316 $[M+Na]^+$

Preparation 76

4-(3-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3140, 1627, 1568, 1465, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 2.29(3H, s), 4.03(sH, s), 7.00-7.21(8H, m),8.45(1H, s)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Preparation 77

Carbon disulfide (0.248 ml) was dropwise added to a solution of 2-isopropyl-6-(2-oxo-2-phenyl-ethyl)-3(2H)-pyridazinone (1.00 g) and sodium hydroxide (343 mg) in a mixture of water (1.15 ml) and dimethyl sulfoxide (5 ml) at 5°C. After 30 minutes, iodomethane (0.607 ml) was dropwise added to the mixture at 5°C and the mixture was stirred at the same temperature for 2 hours. The mixture was poured into water (25 ml) and stirred for 1 hour to give a solid. The solid was dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 60 : 40 v/v) to give 6-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.23 g).

mp: 103-104.5°C (chloroform - n-hexane)

IR (KBr): 1670, 1581 cm^{-1}

ESI/MS: 743$[2M+Na]^+$, 383$[M+Na]^+$, 361$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.17(6H, d, J=6.66 Hz), 2.17(3H, s), 2.42(3H, s), 5.22(1H, 7-plet, J=6.66 Hz), 6.84(1H, d, J=9.82 Hz),

7.41-7.57(3H, m), 7.69(1H, d, J=9.82 Hz), 7.89-7.94(2H, m)
Elemental Analysis for $C_{18}H_{20}N_2O_2S_2$
Calcd.: C,59.97; H,5.59; N,7.77
Found : C,60.08; H,5.58; N,7.78

Preparation 78

6-[1-Benzoyl-2,2-bis(methylthio)vinyl]-2-methyl-3(2H)-pyridazinone was prepared from 2-methyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone, carbon disulfide and methyl iodide according to a similar manner to that of Preparation 77.
mp: 143-146°C (chloroform - hexane)
IR (KBr): 1662, 1581 cm^{-1}
ESI/MS: 687$[2M+Na]^+$, 355$[M+Na]^+$, 333$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 2.14(3H, s), 2.41(3H, s), 3.71(3H, s), 6.87(1H, d, J=9.70 Hz), 7.43-7.58(3H, m), 7.65(1H, d, J=9.70 Hz), 7.90-7.96(2H, m)
Elemental Analysis for $C_{16}H_{16}N_2O_2S_2 \cdot 0.3H_2O$
Calcd.: C,56.88; H,4.95; N,8.29
Found : C,56.83; H,4.76; N,8.36

Preparation 79

6-[1-(4-fluorobenzoyl)-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone, carbon disulfide and methyl iodide according to a similar manner to that of Preparation 77.
mp: 92-94°C (diisopropyl ether)
IR (KBr): 1678-1660, 1597, 1583 cm^{-1}
ESI/MS: 779$[2M+Na]^+$, 401$[M+Na]^+$
^1H NMR ($CDCl_3$, δ): 1.17(6H, d, J=6.60 Hz), 2.18(3H, s), 2.42(3H, s), 5.23(1H, 7-plet, J=6.60 Hz), 6.85(1H, d, J=9.64 Hz), 7.11-7.18(2H, m), 7.69(1H, d, J=9.64 Hz), 7.92-7.98(2H, m)

Preparation 80

1-(4-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared according to a similar manner to that of Preparation 15.

^{1}H NMR (DMSO-d_6, δ): 4.00(3H, s), 4.69(2H, s), 7.21(1H, d, J=9.0 Hz), 7.58(1H, d, J=9.0 Hz), 7.78(2H, d, J=8.6 Hz), 7.99(2H, d, J=8.6 Hz)

ESI/MS: 307, 309$[M+H]^+$, 329, 331$[M+Na]^+$

IR (KBr): 1639, 1585, 1465, 1012 cm^{-1}

Preparation 81

1-(3-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared according to a similar manner to that of Preparation 15

^{1}H NMR (DMSO-d_6, δ): 4.00(3H, s), 4.69(2H, s), 7.21(1H, d, J=9.0 Hz), 7.58(1H, d, J=9.0 Hz), 7.78(2H, d, J=8.6 Hz), 7.99(2H, d, J=8.6 Hz),

ESI/MS: 307, 309$[M+H]^+$, 329, 331$[M+Na]^+$

IR (KBr): 1641, 1558, 1467, 1010 cm^{-1}

Preparation 82

1-(2,6-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl) ethanone was prepared according to a similar manner to that of Preparation 15.

^{1}H NMR (DMSO-d_6, δ): 4.00(3H, s), 4.55(2H, s), 7.14-7.34(3H, m), 7.43-7.72(2H, m)

ESI/MS: 265$[M+H]^+$, 287$[M+Na]^+$

IR (neat): 1648, 1558, 1484 cm^{-1}

Preparation 83

1-(3,5-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl) ethanone was prepared according to a similar manner to that of Preparation 15.

^{1}H NMR (DMSO-d_6, δ): 4.00(3H, s), 4.72(2H, s), 7.22(9.2H, d), 7.31-7.79(4H, m)

ESI/MS: 265$[M+H]^+$, 287$[M+Na]^+$

IR (KBr): 1621, 1594, 1473, 1120 cm^{-1}

Preparation 84

1-(2,6-Dichlorophenyl)-2-(6-methoxy-3-pyridazinyl) ethanone was prepared according to a similar manner to that of Preparation 15.

^1H NMR (DMSO-d_6, δ): 4.02(3H, s), 4.52(2H, s), 7.21-7.64(5H, m)

ESI/MS: 297, 299$[M+H]^+$, 319, 321$[M+Na]^+$

IR (KBr): 1621, 1594, 1473, 1018 cm^{-1}

Preparation 85

1-(2,6-Dimethylphenyl)-2-(6-methoxy-3-pyridazinyl) ethanone was prepared according to a similar manner to that of Preparation 15.

^1H NMR (DMSO-d_6, δ): 2.24(3H, s), 2.28(3H, s), 4.02(2H, s), 7.07-7.30(4H, m), 7.52(1H, m)

ESI/MS: 257$[M+H]^+$, 279$[M+Na]^+$

IR (KBr): 1643, 1540, 1311, 1012 cm^{-1}

Preparation 86

1-(3-Furyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared according to a similar manner to that of Preparation 15.

^1H NMR ($CDCl_3$, δ): 4.12(3H, s), 4.36(2H, s), 6.805(1H, d, J=2 Hz), 6.88(1H, d, J=9.4 Hz), 7.41-7.46(2H, m), 8.26(1H, s),

ESI/MS: 219.3$[M+H]^+$, 241.1$[M+Na]^+$

IR (KBr): 1678, 1598, 1471, 1153 cm^{-1}

Preparation 87

2-(6-Methoxy-3-pyridazinyl)-1-(3-thienyl)ethanone was prepared according to a similar manner to that of Preparation 15.

^1H NMR ($CDCl_3$, δ): 4.11(3H, s), 4.42(2H, s), 6.73(1H, d, J=2 Hz), 6.96(1H, d, J=9.6 Hz), 7.41-7.46(2H, m), 8.40(1H, s)

ESI/MS: 235.1$[M+H]^+$, 257.2$[M+Na]^+$

IR (KBr): 1668, 1602, 1473, 1014 cm^{-1}

Preparation 88

1-(2,6-Dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl) ethanone was prepared according to a similar manner to that of Preparation 43.

^1H NMR (DMSO-d_6, δ): 3.75(6H, s), 4.05(3H, s), 4.28(2H, s), 6.71(2H, d, J=8.4 Hz), 7.18(1H, d, J=9.2 Hz), 7.33(1H, d, J=8.4 Hz), 7.42(1H, d, J=9.2 Hz)

ESI/MS: 289$[M+H]^+$, 311$[M+Na]^+$

IR (KBr): 1716, 1592, 1473, 1110 cm^{-1}

Preparation 89

4-(4-Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^1H NMR (DMSO-d_6, δ): 4.02(3H, s), 7.10(2H, s), 7.07-7.26(2H, m), 7.23(2H, d, J=8.6 Hz), 7.54(2H, d, J=8.6 Hz), 8.69(1H, s)

ESI/MS: 358, 360$[M+H]^+$, 380, 382$[M+Na]^+$

IR (KBr): 3326, 1629, 1583, 1463 cm^{-1}

Preparation 90

4-(3-Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^1H NMR (DMSO-d_6, δ): 4.03(3H, s), 7.10(1H, d, J=9.0 Hz), 7.15(2H, s), 7.25(1H, d, J=9.0 Hz), 7.21-7.61(2H, m), 7.56-7.60(2H, m), 8.51(1H, s),

ESI/MS: 358, 360$[M+H]^+$, 380$[M+Na]^+$

IR (KBr): 3318, 1627, 1529, 1461 cm^{-1}

Preparation 91

4-(2,6-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 3.96(3H, s), 7.13(1H, d, J=9.2 Hz), 7.06-7.14(2H, m), 7.22(2H, s), 7.46(1H, d, J=9.2 Hz), 7.42-7.60(1H, m), 8.64(1H, s)

ESI/MS: 316$[M+H]^+$, 338$[M+Na]^+$

Preparation 92

4-(3,5-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 4.03(3H, s), 6.93-6.98(2H, m), 7.14(1H, d, J=9.2 Hz), 7.18(2H, s), 7.32(1H, d, J=9.2 Hz), 7.24-7.37(1H, m), 8.54(1H, s)

ESI/MS: 316$[M+H]^+$, 338$[M+Na]^+$

IR (KBr): 3478, 1627, 1581, 1459 cm^{-1}

Preparation 93

4-(2,6-Dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 3.96(3H, s), 7.12(1H, d, J=9.4 Hz), 7.22(2H, s), 7.33(1H, d, J=9.4 Hz), 7.30-7.52(3H, m), 8.69(1H, s)

ESI/MS: 348, 350$[M+H]^+$, 370, 372$[M+Na]^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

Preparation 94

4-(2,6-Dimethylphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 1.93(6H, s), 3.97(3H, s), 6.84-7.20(5H, m), 8.64(1H, s)

ESI/MS: 308$[M+H]^+$, 330$[M+Na]^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

Preparation 95

4-(3-Furyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner

to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 4.07(3H, s), 6.32(1H, s), 6.94(2H, s), 7.21(1H, d, J=9.2 Hz), 7.52(1H, d, J=9.2 Hz), 7.55(1H, s), 7.64(1H, s), 8.31(1H, s)

ESI/MS: 270$[M+H]^+$, 292$[M+Na]^+$

IR (KBr): 3168, 1652, 1581, 1461 cm^{-1}

Preparation 96

5-(6-Methoxy-3-pyridazinyl)-4-(3-thienyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 4.05(3H, s), 6.94-6.97(3H, m), 7.13(1H, d, J=9.2 Hz), 7.28(1H, d, J=9.2 Hz), 7.46-7.52(2H, m), 8.39(1H, s)

APCI/MS: 286$[M+H]^+$

IR (KBr): 3191, 1656, 1581, 1461 cm^{-1}

Preparation 97

4-(2,6-Dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared according to a similar manner to that of Preparation 60.

^{1}H NMR (DMSO-d_6, δ): 3.55(6H, s), 3.97(3H, s), 6.64(2H, d, J=8.6 Hz), 6.91(2H, s), 6.96-7.02(2H, m), 7.31(1H, t, J=5.6 Hz), 8.52(1H, s)

ESI/MS: 340$[M+H]^+$, 340$[M+Na]^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

Example 1

A mixture of 2-amino-5-(6-methoxy-3-pyridazinyl)-4-phenylpyrimidine (5.41 g), conc. HCl (0.1 ml) and 4N HCl/dioxane (48.5 ml) in dioxane (54 ml) was heated to 110°C for 1.5 hours. The reaction mixture was poured into ice/water and pH was adjusted to circa 7-8 with aqueous sodium hydroxide solution. Precipitates were collected by filtration, washed with water and dried to give a crude material, which was recrystallized from 90% aqueous

EtOH to give
6-(2-amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (4.34 g) as colorless crystals.
mp: > 280°C
IR (Nujol): 3269, 1676, 1651 cm^{-1}
NMR (DMSO-d_6, δ): 6.67(1H, d, J=9.8 Hz), 6.87(1H, d, J=9.8 Hz), 7.04(2H, brd. s), 7.37-7.44(5H, m), 8.39(1H, s), 13.07(1H, s),
ESI/MS: 288 $[M+Na]^+$
Elemental Analysis for $C_{14}H_{11}N_5O$
Calcd.: C,63.39; H,4.18; N,26.40
Found : C,63.55; H,4.24; N,26.32

Example 2

A suspension of 6-(2-amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (503 mg) in DMF (10 ml) was cooled in an ice/water bath and 60% NaH (83.9 mg) was added to the mixture. After the mixture was stirred for 15 mimutes, isopropyl iodide was added and the mixture was stirred at ambient temperature overnight. The mixture was poured into ice/water and resultant precipitates were filtered, washed with water, and dried to give 430 mg of powder, which was then purified by silica-gel column chromatography ($CHCl_3$-MeOH, 50:1) to give 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (354 mg) as colorless crystals.
mp: 216-217°C (90% aqueous EtOH)
IR (Nujol): 3356, 3313, 3170, 1671, 1651 cm^{-1}
NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 4.97-5.10(1H, m), 6.80(1H, d, J=9.6 Hz), 7.06(2H, brd. s), 7.18(1H, d, J=9.6 Hz), 7.31-7.41(5H, m), 8.46(1H, s)
ESI/MS: 330 $[M+Na]^+$
Elemental Analysis for $C_{17}H_{17}N_5O$
Calcd.: C,66.43; H,5.58; N,22.79
Found : C,66.17; H,5.58; N,22.69

Example 3

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 254-255°C (90% aqueous EtOH)

IR (Nujol): 3313, 3168, 1670, 1649 cm^{-1}

NMR (DMSO-d_6, δ): 3.65(3H, s), 6.71(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.08(2H, brd. s), 7.38-7.46 (5H, m), 8.42(1H, s)

ESI/MS: 302 $[M+Na]^+$

Elemental Analysis for $C_{15}H_{13}N_5O$

Calcd.: C,64.51; H,4.69; N,25.08

Found : C,64.32; H,4.75; N,24.91

Example 4

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-ethyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 255-256°C (90% aqueous EtOH)

IR (Nujol): 1649 cm^{-1}

NMR (DMSO-d_6, δ): 1.13(3H, t, J=7.2 Hz), 4.01(2H, q, J=7.2 Hz), 6.75(1H, d, J=9.6 Hz), 6.99(1H, d, J=9.6 Hz), 7.07(2H, brd. s), 7.35-7.43(5H, m), 8.44(1H, s)

ESI/MS: 316 $[M+Na]^+$

Elemental Analysis for $C_{16}H_{15}N_5O$

Calcd.: C,65.52; H,5.15; N,23.88

Found : C,65.48; H,5.21; N,23.78

Example 5

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-propyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 188-189°C (90% aqueous EtOH)

IR (Nujol): 1651 cm^{-1}

NMR (DMSO-d_6, δ): 0.80(3H, t, J=7.4 Hz), 1.48-1.66(2H, m), 3.96(2H, t, J=7.2 Hz), 6.75(1H, d, J=9.6 Hz), 6.99(1H, d, J=9.6 Hz), 7.07(2H, brd. s), 7.34-7.43(5H, m), 8.42(1H, s)

ESI/MS: 330 $[M+Na]^+$

Elemental Analysis for $C_{17}H_{17}N_5O$

Calcd.: C,66.43; H,5.58; N,22.79

Found : C,66.25; H,5.61; N,22.72

Example 6

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-benzyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 229-230°C (90% aqueous EtOH)

IR (Nujol): 3353, 3324, 3191, 1670, 1651 cm^{-1}

NMR (DMSO-d_6, δ): 5.19(2H, s), 6.80(1H, d, J=9.6 Hz), 7.01(1H, d, J=9.6 Hz), 7.08(2H, brd. s), 7.17-7.46(10H, m), 8.38(1H, s)

ESI/MS: 378 $[M+Na]^+$

Elemental Analysis for $C_{21}H_{17}N_5O$

Calcd.: C,70.97; H,4.82; N,19.71

Found : C,70.85; H,4.92; N,19.68

Example 7

A solution of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (177 mg) in pyridine (1.8 ml) was cooled in an ice/water bath. Acetyl chloride (49.7 mg) was added to the solution and the mixture was stirred at ambient temperature for 4 hours. Pyridine was removed under reduced pressure and the residue was partitioned between water and $CHCl_3$. After an additional extraction with $CHCl_3$, the combined extracts were washed with saturated sodium hydrogencarbonate solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by silica-gel column chromatography ($CHCl_3$-MeOH, 50:1) to give N-[5-(1-isopropyl-6-oxo-1,6-dihydro-

3-pyridazinyl)-4-phenyl-2-pyrimidinyl]acetamide (107 mg) as colorless crystals.

mp: 209-210°C (90% aqueous EtOH)

IR (Nujol): 3157, 3128, 1670, 1652 cm^{-1}

NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 2.27(3H, s), 5.02-5.08(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.44(5H, s), 8.85(1H, s), 10.79(1H, s),

ESI/MS: 349 $[M+Na]^+$

Elemental Analysis for $C_{19}H_{19}N_5O_2$

Calcd.: C,65.32; H,5.48; N,20.04

Found : C,65.27; H,5.53; N,19.86

Example 8

6-[2-(Methylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone was obtained from 5-(6-methoxy-3-pyridazinyl)-N-methyl-4-phenyl-2-pyrimidinamine according to a similar manner to that of Example 1.

mp: >255°C (90% aqueous EtOH)

IR (Nujol): 3311, 1670, 1651 cm^{-1}

NMR (DMSO-d_6, δ): 2.89(3H, d, J=4.7 Hz), 6.67(1H, d, J=9.7 Hz), 6.87(1H, d, J=9.7 Hz), 7.42-7.51(6H, m), 8.43(1H, brd. s), 13.07(1H, brd. s)

ESI/MS: 302 $[M+Na]^+$

Elemental Analysis for $C_{15}H_{13}N_5O$

Calcd.: C,64.51; H,4.69; N,25.08

Found : C,64.39; H,4.72; N,24.92

Example 9

6-[2-(Dimethylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone was obtained from 5-(6-methoxy-3-pyridazinyl)-N,N-dimethyl-4-phenyl-2-pyrimidinamine according to a similar manner to that of Example 1.

mp: 245-246°C (90% aqueous EtOH)

IR (Nujol): 3213, 1674, 1650 cm^{-1}

NMR (DMSO-d_6, δ): 3.22(6H, s), 6.69(1H, d, J=9.8 Hz), 6.88(1H, d, J=9.8 Hz), 7.38-7.50(5H, m), 8.49(1H, s), 13.09(1H, brd. s)

ESI/MS: 316 $[M+Na]^+$

Elemental Analysis for $C_{16}H_{15}N_5O$

Calcd.: C,65.52; H,5.15; N,23.88

Found : C,65.44; H,5.12; N,23.85

Example 10

2-Isopropyl-6-[2-(methylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone was obtained from 6-[2-(methylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone according to a similar manner to that of Example 2.

mp: 160-161°C (EtOAc)

IR (Nujol): 1651 cm^{-1}

NMR (DMSO-d_6, δ): 1.03(6H, d, J=6.5 Hz), 2.89(3H, d, J=4.8 Hz), 5.02-5.05(1H, m), 6.81(1H, d, J=9.6 Hz), 7.19(1H, d, J=9.6 Hz), 7.39(5H, brd. s), 7.54(1H, brd. s), 8.50(1H, brd. s)

ESI/MS: 322 $[M+H]^+$, 344 $[M+Na]^+$

Elemental Analysis for $C_{18}H_{19}N_5O$

Calcd.: C,67.27; H,5.96; N,21.79

Found : C,67.26; H,6.01; N,21.75

Example 11

6-[2-(Dimethylamino)-4-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was obtained from 6-[2-(dimethylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone according to a similar manner to that of Example 2.

mp: 155-156°C (EtOAc)

IR (Nujol): 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ): 1.03(6H, d, J=6.6Hz), 3.22(6H, s), 5.02-5.05(1H, m), 6.83(1H, d, J=9.6 Hz), 7.20(1H, m, J=9.6 Hz), 7.40(5H, s), 8.56(1H, s).

ESI/MS: 336 $[M+H]^+$, 358 $[M+Na]^+$

Elemental Analysis for $C_{19}H_{21}N_5O$
Calcd.: C,68.04; H,6.31; N,20.88
Found : C,68.01; H,6.34; N,20.87

Example 12

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was obtained from 2-isopropyl-6-(2-oxo-2-phenylethyl)-(2H)-pyridazinone according to a similar manner to that of Preparation 3.
mp: 216-217°C (90% aqueous EtOH).

Example 13

(1)

To a mixture of 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone (1.65 g) and N,N-dimethylformamide dimethyl acetal (1.6 ml) was heated at 100-105°C for 30 minutes. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (MeOH-EtOAc, 1:99 v/v) to give a stereomixture of 6-[2-(dimethylamino)-1-(4-fluorobenzoyl)-ethenyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.57 g).
mp: 161-162.5°C (chloroform - n-hexane)
IR (KBr) : 1647, 1626, 1581, 1552cm^{-1}
^1H NMR ($CDCl_3$, δ) : major product 1.32(6H, d, J=6.67 Hz), 2.90(6H, s), 5.33(1H, 7-plet, J=6.67 Hz), 6.76(1H, d, J=9.48 Hz), 6.95-7.11(3H, m), 7.43-7.52(3H, m);
minor product 1.24(6H, d, J=6.60 Hz), 2.99(6H, s)
ESI/MS: 681 $[2M+Na]^+$, 352 $[M+Na]^+$, 330$[M+H]^+$
Elemental Analysis for $C_{18}H_{20}FN_3O_2$
Calcd.: C,65.64; H,6.12; N,12.76
Found : C,65.35; H,6.38; N,12.58

(2)

To a solution of potassium t-butoxide (80.8 mg) in methanol (0.6 ml), guanidine hydrochloride (68.8 mg) was added under

ice-cooling. After 15 minutes, a stereomixture of 6-[2-(dimethylamino)-1-(4-fluorobenzoyl)ethenyl]-2-isopropy l-3(2H)-pyridazinone (198 mg) was added and heated under reflux for 4 hours. Water was added to a reaction mixture. After stirring, an aqueous layer was removed by decantation to give a residue. The residue was dissolved in chloroform, dried over magnesium sulfate, concentrated under reduced pressure and was recrystallized from a mixture of chloroform and hexane to give 6-[2-amino-4-(4-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (138 mg).

mp: 238-239°C (ethanol-isopropyl ether)

IR (KBr) : 3413, 3182, 1647, 1577, 1492 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.31(6H, d, J=6.62 Hz), 5.33(1H, 7-plet, J=6.62 Hz), 5.37(2H, br.s), 6.70(1H, d, J=9.56 Hz), 6.74(1H, d, J=9.56 Hz), 7.05-7.10(2H, m), 7.40-7.45(2H, m), 8.51(1H, s)

ESI/MS: 673 $[2M+Na]^+$, 348 $[M+Na]^+$, 326 $[M+H]^+$

Elemental Analysis for $C_{17}H_{16}FN_5O$

Calcd.: C,62.76; H,4.96; N,21.53

Found : C,62.76; H,4.90; N,21.54

Example 14

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 1.

NMR (DMSO-d_6, δ): 6.68(1H, d, J=9.8 Hz), 6.95(1H, d, J=9.8 Hz), 7.14(2H, brd. s), 7.32-7.47(3H, m), 7.63(1H, d, J=7.9 Hz), 8.50(1H, s), 13.0(1H, brd. s)

ESI/MS: 366, 368 $[M+Na]^+$

Example 15

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 203-205°C (EtOH)

IR (Nujol): 3396, 3319, 3197, 1649, 1630, 1579, 1560 cm^{-1}

NMR (DMSO-d_6, δ): 0.86(6H, d, J=6.4 Hz), 4.87-5.00(1H, m), 6.85(1H, d, J=9.7 Hz), 7.15(2H, brd. s), 7.29-7.58(4H, m), 7.60(1H, d, J=7.4 Hz), 8.57(1H, s)

ESI/MS: 408, 410 $[M+Na]^+$

Example 16

A suspension of 6-[2-amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (138 mg), 10% palladium on carbon (19.7 mg) and sodium acetate (58.6 mg) in methanol(14 ml) was hydrogenated at 20°C under hydrogen atmosphere for 8 hours. Insoluble material was filtered off and the solvent was removed under reduced pressure. The residue was partitioned between sodium bicarbonate solution and dichloromethane. After additional extraction with dichloromethane (x2), the combined extracts were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to afford colorless crystals of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone.

Example 17

A solution of 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone (177 mg) and morpholine (0.0653 ml) in dioxane (0.35 ml) was heated at 100-105°C for 25 hours. Water (3.5 ml) was added to the reaction mixture to give a solid. The solid was collected by filltration, dissolved in chloroform, dried over magnesium sulfate and purified by column chromatography on silica gel (methanol - chloroform 1 : 99 v/v) to give 2-isopropyl-6-[2-morpholino-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (125 mg).

mp: 200.5-202°C (ethanol - diisopropyl ether)

IR (KBr): 1666, 1591, 1574, 1514 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.31(6H, d, J=6.64 Hz), 3.77-3.83(4H, m), 3.91-3.97(4H, m), 5.31(1H, 7-plet, J=6.64 Hz), 6.66(1H, d,

J=9.54 Hz), 6.71(1H, d, J=9.54 Hz), 7.33-7.48(5H, m), 8.56(1H, s)

ESI/MS: 777 $[2M+Na]^+$, 400 $[M+Na]^+$, 378 $[M+H]^+$

Elemental Analysis for $C_{21}H_{23}N_5O_2$

Calcd.: C,66.83; H,6.14; N,18.55

Found : C,66.84; H,6.33; N,18.48

Example 18

2-Isopropyl-6-{4-phenyl-2-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone and 2-pyridinylmethylamine according to a similar manner to that of Example 17.

mp: 143-144.5°C (ethanol - diisopropyl ether)

IR (KBr): 3275, 1660, 1587, 1576 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.31(6H, d, J=6.62 Hz), 4.86(2H, d, J=5.46 Hz), 5.31(1H, 7-plet, J=6.62 Hz), 6.45-6.49(1H, m), 6.66(1H, d, J=9.60 Hz), 6.70(1H, d, J=9.60 Hz), 7.17-7.24(1H, m), 7.33-7.68(6H, m), 7.63-7.73(1H, m), 8.55-8.61(2H, m)

ESI/MS: 421 $[M+Na]^+$, 399 $[M+H]^+$

Elemental Analysis for $C_{23}H_{22}N_6O \cdot 0.2H_2O$

Calcd.: C,68.71; H,5.62; N,20.90

Found : C,68.65; H,5.65; N,20.88

Example 19

6-(2-Anilino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone and aniline according to a similar manner to that of Example 17.

mp: 200-202°C (ethanol - diisopropyl ether)

IR (KBr): 1662, 1587, 1568 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.33(6H, d, J=6.62 Hz), 5.32(1H, 7-plet, J=6.62 Hz), 6.69(1H, d, J=9.55 Hz), 6.74(1H, d, J=9.55 Hz),

7.08(1H, t, J=7.42 Hz), 7.32-7.52(9H, m), 7.70(1H, d, J=7.68 Hz), 8.66(1H, s)

ESI/MS: 789 $[2M+Na]^+$, 406 $[M+Na]^+$, 384 $[M+H]^+$

Elemental Analysis for $C_{23}H_{21}N_5O$

Calcd.: C,72.04; H,5.52; N,18.26

Found : C,71.88; H,5.58; N,18.17

Example 20

6-[2-Amino-4-(2-fluorophenyl)-5-pyrimidinyl]-2-isopropy l-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(2-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 239-240.5°C (ethanol)

IR (KBr): 3392, 3325, 3203, 1649, 1633, 1585 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.11(6H, d, J=6.60 Hz), 5.20(1H, 7-plet, J=6.60 Hz), 5.45(2H, br.s), 6.79(1H, d, J=9.56 Hz), 6.94-7.04(2H, m), 7.20-7.55(3H, m), 8.51(1H, s)

ESI/MS: 673 $[2M+Na]^+$, 348 $[M+Na]^+$, 326 $[M+H]^+$

Elemental Analysis for $C_{17}H_{16}FN_5O$

Calcd.: C,62.76; H,4.96; N,21.53

Found : C,62.74; H,5.07; N,21.39

Example 21

6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-2-isopropy l-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(3-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 220-221.5°C (ethanol)

IR (KBr): 3425, 3305, 3194, 1660, 1637, 1581 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.29(6H, d, J=6.60 Hz), 5.30(1H, 7-plet, J=6.60 Hz), 5.39(2H, br.s), 6.73(1H, d, J=9.56 Hz), 6.78(1H, d, J=9.56 Hz), 7.09-7.33(4H, m), 8.53(1H, s)

ESI/MS: 673 $[2M+Na]^+$, 348 $[M+Na]^+$, 326 $[M+H]^+$

Elemental Analysis for $C_{17}H_{16}FN_5O$
Calcd.: C,62.76; H,4.96; N,21.53
Found : C,62.77; H,5.02; N,21.55

Example 22

6-[2-Amino-4-(2-chlorophenyl)-5-pyrimidinyl]-2-isopropy l-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(2-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 227-228.5°C (ethanol)
IR (KBr): 3398, 3327, 3201, 1649, 1631 cm^{-1}
^1H NMR (DMSO-d_6, δ): 0.85(6H, d, J=6.58 Hz), 5.30(1H, 7-plet, J=6.58 Hz), 6.86(1H, d, J=9.58 Hz), 7.15(2H, br.s), 7.33-(4H, m), 7.48(1H, d, J=9.58 Hz), 8.57(1H, s)
ESI/MS: 707 and 705 $[2M+Na]^+$, 366 and 364 $[M+Na]^+$, 344 and 342 $[M+H]^+$ (mobile phase MeOH-H_2O)
Elemental Analysis for $C_{17}H_{16}ClN_5O$
Calcd.: C,59.74; H,4.72; N,20.49
Found : C,59.92; H,4.79; N,20.45

Example 23

6-[2-Amino-4-(3-chlorophenyl)-5-pyrimidinyl]-2-isopropyl -3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(3-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 236-237°C (ethanol)
IR (KBr): 3471, 3298, 3180, 1664, 1622, 1585 cm^{-1}
^1H NMR ($CDCl_3$, δ) : 1.28(6H, d, J=6.62 Hz), 5.30(1H, 7-plet, J=6.62 Hz), 5.37(2H, br.s), 6.74(1H, d, J=9.54 Hz), 6.79(1H, d, J=9.54 Hz), 7.17-7.42(3H, m), 7.51-7.53(1H, m), 8.53(1H, s)
ESI/MS: 707 and 705 $[2M+Na]^+$, 366 and 364 $[M+Na]^+$, 344 and 342 $[M+H]^+$

Elemental Analysis for $C_{17}H_{16}ClN_5O$
Calcd.: C,59.74; H,4.72; N,20.49
Found : C,59.58; H,4.76; N,20.41

Example 24

6-{2-Amino-4-[2-(trifluoromethyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-{2-(dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).
mp: 160-161°C (ethanol - hexane)
IR (KBr): 3411, 3329, 3207, 1649, 1630, 1583 cm^{-1}
^1H NMR ($CDCl_3$, δ) : 1.07(6H, d, J=6.62 Hz), 5.18(1H, 7-plet, J=6.62 Hz), 5.35(2H, br.s), 6.73(1H, d, J=9.56 Hz), 6.92(1H, d, J=9.56 Hz), 7.24-7.29(1H, m), 7.47-7.61(2H, m), 7.71-7.77(1H, m), 8.57(1H, s)
ESI/MS: 773 $[2M+Na]^+$, 398 $[M+Na]^+$
Elemental Analysis for $C_{18}H_{16}F_3N_5O$
Calcd.: C,57.60; H,4.30; N,18.66
Found : C,57.86; H,4.29; N,18.72

Example 25

6-{2-Amino-4-[3-(trifluoromethyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-{2-(dimethylamino)-1-[3-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).
mp: 163.5-165°C (ethanol - hexane)
IR (KBr): 3454, 3305, 3178, 1662, 1630, 1585 cm^{-1}
^1H NMR ($CDCl_3$, δ) : 1.23(6H, d, J=6.62 Hz), 5.28(1H, 7-plet, J=6.62 Hz), 5.41(2H, br.s), 6.75(1H, d, J=9.56 Hz), 6.82(1H, d, J=9.56 Hz), 7.44-7.57(2H, m), 7.65-7.69(1H, m), 7.78(1H, br.s), 8.53(1H, s)
ESI/MS: 773 $[2M+Na]^+$, 398 $[M+Na]^+$, 376 $[M+H]^+$
Elemental Analysis for $C_{18}H_{16}F_3N_5O$

Calcd.: C,57.60; H,4.30; N,18.66

Found : C,57.67; H,4.36; N,18.52

Example 26

6-{2-Amino-4-[4-(trifluoromethyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-{2-(dimethylamino)-1-[4-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 209-210.5°C (ethanol - hexane)

IR (KBr): 3338, 3311, 3180, 1643, 1583 cm^{-1}

^1H NMR ($CDCl_3$, δ) : 1.20(6H, d, J=6.62 Hz), 5.27(1H, 7-plet, J=6.62 Hz), 5.42(2H, br.s), 6.76(1H, d, J=9.54 Hz), 6.84(1H, d, J=9.54 Hz), 7.53(2H, d, J=8.26 Hz), 7.65(2H, d, J=8.26 Hz), 8.54(1H, s)

ESI/MS: 773 $[2M+Na]^+$, 398 $[M+Na]^+$, 376 $[M+H]^+$

Elemental Analysis for $C_{18}H_{16}F_3N_5O$

Calcd.: C,57.60; H,4.30; N,18.66

Found : C,57.81; H,4.29; N,18.79

Example 27

4-(4-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine (309 mg) was dissolved in c-hydrochloric acid (5 ml) and dioxane (20 ml). The solution was heated at 55°C, and stirred overnight. Evaporation of solvent in vacuo gave a residue. To the residue was added water (10 ml). The pH of the supension was adjusted to 7-8 with 1N-sodium hydroxide solution. The crystals were collected by filtration ,washed with water, dried in vacuo, to give 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone (285 mg).

mp: 142°C (water)

IR (KBr): 3409, 1639, 1585, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 3.78(3H, s), 6.95(1H, d, J=9.8 Hz), 6.89(1H, d, J=9.8 Hz), 6.97(1H, d, J=9.0 Hz), 6.99(1H, s), 7.36(1H,

d, J=9.0 Hz), 8.33(1H, s), 13.1(1H, s)

ESI/MS: 296 $[M+H]^+$

Example 28

6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-fluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 249°C (water)

IR (KBr): 3156, 1677, 1577, 1440, 1263 cm^{-1}

NMR (DMSO-d_6, δ): 6.73(1H, d, J=9.8 Hz), 6.98(1H, d, J=9.8 Hz), 7.12-7.45(7H, m), 8.42(1H, s), 13.1(1H, s)

ESI/MS: 284 $[M+H]^+$

Example 29

6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-fluoro-4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 250°C (water)

IR (KBr): 3164, 1654, 1550, 1417, 1238 cm^{-1}

NMR (DMSO-d_6, δ): 3.85(3H, s), 6.73(1H, d, J=9.8 Hz), 6.98(1H, d, J=9.8 Hz), 7.06(2H, s), 7.14-7.36(4H, m), 8.36(1H, s), 13.1(1H, s)

ESI/MS: 314 $[M+H]^+$

Example 30

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(4-chlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

IR (KBr): 3317, 1630, 1566, 1481, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 6.74(1H, d, J=9.8 Hz), 6.97(1H, d, J=9.8 Hz),

7.11(1H, s), 7.32-7.51(4H, m), 8.40(1H, s), 13.1(1H, s)
ESI/MS: 300 and 302 $[M+H]^+$

Example 31

6-[2-Amino-4-(3-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(3-pyridinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.
mp: 256°C (water)
IR (KBr): 3170, 1646, 1550, 1409, 1220 cm^{-1}
NMR (DMSO-d_6, δ): 6.76(1H, d, J=9.8 Hz), 7.09(1H, d, J=9.8 Hz), 7.16(2H, s), 7.40-7.48(1H, m), 7.73-7.79(1H, m), 8.44(1H, s), 8.57-8.61(2H, m), 13.1(1H, brs)
ESI/MS: 265 $[M-H]^-$

Example 32

6-[2-Amino-4-(4-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(4-pyridinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.
IR (KBr): 3295, 1658, 1585, 1411, 1236 cm^{-1}
NMR (DMSO-d_6, δ): 6.77(1H, d, J=9.8 Hz), 7.11(1H, d, J=9.8 Hz), 7.21(2H, s), 7.33-7.36(2H, m), 8.47(1H, s), 8.60-8.63(2H, m), 13.0(1H, s)
ESI/MS: 265 $[M-H]^-$

Example 33

6-[2-Amino-4-(1,3-thiazol-2-yl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(1,3-thiazol-2-yl)-2-pyrimidinamine according to a similar manner to that of Example 27.
IR (KBr): 3324, 1633, 1531, 1442, 1228 cm^{-1}
NMR (DMSO-d_6, δ): 6.75(1H, d, J=9.8 Hz), 7.22(2H, s), 7.34(1H, d, J=9.8 Hz), 7.89-8.04(2H, m), 8.38(1H, s), 13.3(1H, s)
ESI/MS: 273 $[M+H]^+$, 295 $[M+Na]^+$

Example 34

6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(2-furyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 262-268°C(water)

IR (KBr): 3342, 1629, 1573, 1471, 1224 cm^{-1}

NMR (DMSO-d_6, δ): 6.61-6.64(1H, m), 6.82-6.93(2H, m), 7.01(2H, s), 7.26(1H, d, J=9.8 Hz), 7.78(1H, s), 8.28(1H, s), 13.1(1H, s)

ESI/MS: 278 $[M+Na]^+$

Example 35

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(4-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 249°C (water)

IR (KBr): 3154, 1641, 1583, 1481, 1226 cm^{-1}

NMR (DMSO-d_6, δ): 2.32(3H, s), 6.68(1H, d, J=9.8 Hz), 6.88(1H, d, J=9.8 Hz), 7.03(2H, s), 7.20(2H, d, J=8.0 Hz), 7.30(2H, d, J=8.0 Hz), 8.37(1H, s), 13.1(1H, s)

ESI/MS: 280 $[M+H]^+$, 302 $[M+Na]^+$

Example 36

6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 307°C (water)

IR(KBr): 3334, 1681, 1589, 1482, 1232 cm^{-1}

NMR (DMSO-d_6, δ): 6.75(1H, d, J=9.8 Hz), 7.03(1H, d, J=9.8 Hz), 7.14-7.19(2H, m), 7.40-7.94(3H, m), 8.43(1H, s), 13.1(1H, s)

ESI/MS: 301 $[M+H]^+$, 323 $[M+Na]^+$

Example 37

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 225°C (water)

IR (KBr): 3174, 1644, 1587, 1425, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 3.68(3H, s), 3.77(3H, s), 6.70(1H, d, J=9.8 Hz), 6.86-7.10(6H, m), 8.34(1H, s), 13.1(1H, s)

ESI/MS: 326 $[M+H]^+$, 348 $[M+Na]^+$

Example 38

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 300°C (water)

IR (KBr): 3321, 1681, 1583, 1475, 1226 cm^{-1}

NMR (DMSO-d_6, δ): 6.78(1H, d, J=9.8 Hz), 7.11(1H, d, J=9.8 Hz), 7.17(2H, brs), 7.26(1H, d, J=8.4 Hz), 7.69(1H, d, J=8.4 Hz), 7.71(1H, d, J=2.0 Hz), 8.43(1H, s), 13.1(1H, s)

ESI/MS: 356, 358 and 360 $[M+Na]^+$

Example 39

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(2-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 313°C (water)

IR (KBr): 3378, 1643, 1581, 1490, 1234 cm^{-1}

NMR (DMSO-d_6, δ): 2.06(3H, s), 6.57(1H, d, J=9.8 Hz), 6.72(1H, d, J=9.8 Hz), 7.08-7.32(4H, m), 8.44(1H, s), 13.04(1H, s)

ESI/MS: 302 $[M+Na]^+$

Example 40

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(2-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 273°C (water)

IR (KBr): 3365, 1646, 1575, 1490, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 3.57(3H, s), 6.66(1H, d, J=9.8 Hz), 6.91(1H, d, J=9.8 Hz), 7.00(2H, s), 6.98-7.07(2H, m), 7.36-7.45(2H, m), 8.35(1H, s), 12.09(1H, s)

ESI/MS: 318 $[M+Na]^+$

Example 41

6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(2-thienyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 265°C (water)

IR(KBr): 3330, 1654, 1523, 1430, 1213 cm^{-1}

NMR (DMSO-d_6, δ): 6.87(1H, d, J=9.8 Hz), 7.00-7.10(2H, m), 7.01(2H, s), 7.26(1H, d, J=9.8 Hz), 7.73(1H, s), 8.28(1H, s), 13.1(1H, s)

ESI/MS: 294 $[M+Na]^+$

Example 42

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(3-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp : 216°C (water)

IR (KBr): 3403, 1641, 1575, 1442, 1207 cm^{-1}

NMR (DMSO-d_6, δ): 2.30(3H, s), 6.58(1H, d, J=9.8 Hz), 6.86(1H, d, J=9.8 Hz), 7.05(2H, s), 7.09-7.40(4H, m), 8.38(1H, s), 13.08(1H, s)

ESI/MS: 302 $[M+Na]^+$

Example 43

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 134°C (water)

IR (KBr): 3336, 1671, 1575, 1491, 1216 cm^{-1}

NMR (DMSO-d_6, δ): 3.72(3H, s), 6.68(1H, d, J=9.8 Hz), 6.88(1H, d, J=9.8 Hz), 7.02(2H, s), 6.87-7.07(2H, m), 7.26-7.43(2H, m), 8.38(1H, s), 13.1(1H, s)

ESI/MS: 318 $[M+Na]^+$

Example 44

6-[2-Amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone (59.0 mg) was dissolved in dimethylformamide(5 ml). To the solution was added potassium t-butoxide (29.2 mg) and isopropyl iodide(44.2 mg). The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was portioned to ethyl acetate and water. The organic layer was separated and washed with brine. The combined aqueous layer was extracted with ethyl acetate. The combined organic layer was passed to diatomaceous earth column. The organic solution was concentrated under reduced pressure to give a residue. The above residue was purified by column chromatography on silica gel (chloroform (100%) and chloroform-methanol (95:5)). The fraction containing product was concentrated under reduced pressure to give crystal residue. The residue was recrystallized from ethanol-water(4:1) to give 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (44.0 mg).

mp: 216.5°C (ethanol-water)

IR (KBr): 3477, 1650, 1555, 1481, 1411 cm^{-1}

NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6Hz), 3.76(3H, s), 5.02-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.94(2H, d, J=6.8 Hz), 6.98(2H,

s), 7.08(1H, d, J=9.6 Hz), 7.32(2H, d, J=6.8 Hz), 8.38(1H, s)

ESI/MS: 338 $[M+H]^+$, 360 $[M+Na]^+$

Example 45

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 195°C (ethanol-water)

IR (KBr): 3477, 1658, 1550, 1488, 1411 cm^{-1}

NMR (DMSO-d_6, δ): 1.02(6H, d, J=6.6 Hz), 4.96-5.10(1H, m), 6.85(1H, d, J=9.6 Hz), 7.12(2H, s), 7.28(1H, d, J=9.6 Hz), 7.35(2H, d, J=6.6 Hz), 7.47(2H, d, J=6.6 Hz), 8.47(1H, s)

ESI/MS: 342 and 344 $[M+H]^+$, 364 and 366 $[M+Na]^+$

Example 46

6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 174°C (ethanol-water)

IR (KBr): 3477, 1650, 1555, 1481, 1411 cm^{-1}

NMR (DMSO-d_6, δ): 1.11(6H, d, J=6.6 Hz), 3.84(3H, s), 5.01-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.94(2H, d, J=6.8 Hz), 6.98(2H, s), 7.08(1H, d, J=9.6 Hz), 7.32(2H, d, J=6.8 Hz), 8.38(1H, s)

ESI/MS: 356 $[M+H]^+$, 378 $[M+Na]^+$

Example 47

6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 215°C (ethanol-water)

IR(KBr): 3318, 1668, 1646, 1590, 1533 cm^{-1}

NMR (DMSO-d_6, δ): 1.30(6H, d, J=6.8 Hz), 5.09-5.20(1H, m), 6.60-6.62(1H, m), 6.87-6.92(2H, m), 7.03(2H, s), 7.32(1H, d, J=9.6 Hz), 7.60(1H, d, J=1.2 Hz), 8.33(1H, s)

ESI/MS: 298 $[M+H]^+$, 320 $[M+Na]^+$

Example 48

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 224°C (ethanol-water)

IR (KBr): 3467, 1633, 1567, 1482, 1411 cm^{-1}

NMR (DMSO-d_6, δ): 1.10(6H, d, J=6.6 Hz), 2.30(3H, s), 5.03-5.09(1H, m), 6.80(1H, d, J=9.6 Hz), 7.04(2H, s), 7.09(1H, d, J=9.6 Hz), 7.16-7.27(4H, m), 8.41(1H, s)

ESI/MS: 322 $[M+H]^+$, 344 $[M+Na]^+$

Example 49

6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 208°C (ethanol-water)

IR (KBr): 3405, 1643, 1581, 1515, 1490, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 1.02(6H, d, J=6.6 Hz), 4.97-5.10(1H, m), 6.87(1H, d, J=9.6 Hz), 7.06(2H, s), 7.34(1H, d, J=9.6 Hz), 7.39-7.53(3H, m), 8.49(1H, s)

ESI/MS: 344 $[M+H]^+$, 366 $[M+Na]^+$

Example 50

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-2-

isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 176°C (ethanol-water)

IR(KBr): 3342, 1645, 1581, 1483, 1409 cm^{-1}

NMR (DMSO-d_6, δ): 0.98(6H, d, J=6.6Hz), 4.96-5.09(1H, m), 6.90(1H, d, J=9.6 Hz), 7.19(2H, s), 7.26(1H, dd, J=2,8.2 Hz), 7.36(1H, d, J=9.6 Hz), 7.61-7.67(2H, m), 8.51(1H, s)

ESI/MS: 376, 378 and 380 $[M+H]^+$, 398, 400 and 402 $[M+Na]^+$

Example 51

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 167°C (ethanol-water)

IR(KBr): 3390, 1659, 1639, 1575, 1465, 1265 cm^{-1}

NMR (DMSO-d_6, δ): 1.17(6H, d, J=6.6 Hz), 3.63(3H, s), 3.76(3H, s), 5.07-5.17(1H, m), 6.78(1H, d, J=9.6 Hz), 6.88-7.04(6H, m), 8.38(1H, s)

ESI/MS: 368 $[M+H]^+$, 390 $[M+Na]^+$

Example 52

6-[2-Amino-4-(3-pyridinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 204°C (ethanol-water)

IR (KBr): 3343, 1654, 1589, 1550, 1290 cm^{-1}

NMR (DMSO-d_6, δ): 0.94(6H, d, J=6.6Hz), 4.92-5.06(1H, m), 6.89(1H, d, J=9.6 Hz), 7.17(2H, s), 7.39-7.46(2H, m), 7.71-7.78(1H, m), 8.50-8.58(3H, m)

ESI/MS: 309 $[M+H]^+$, 331 $[M+Na]^+$

Example 53

6-[2-Amino-4-(4-pyridinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 219°C (ethanol-water)

IR (KBr): 3343, 1662, 1644, 1585, 1482, 1216 cm^{-1}

NMR (DMSO-d_6, δ): 0.88(6H, d, J=6.6 Hz), 4.91-5.04(1H, m), 6.90(1H, d, J=9.6 Hz), 7.21(2H, s), 7.25-7.31(2H, m), 7.47(1H, d, J=9.6 Hz), 8.56-8.61(3H, m)

ESI/MS: 309 $[M+H]^+$, 331 $[M+Na]^+$

Example 54

6-[2-Amino-4-(1,3-thiazol-2-yl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(1,3-thiazol-2-yl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

IR (KBr): 3324, 1689, 1633, 1589, 1531, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 1.23(6H, d, J=6.6 Hz), 5.09-5.19(1H, m), 6.80(1H, d, J=9.6 Hz), 7.24(2H, s), 7.38(1H, d, J=9.6 Hz), 7.89(1H, d, J=3.2 Hz), 7.93(1H, d, J=3.2 Hz), 8.43(1H, s)

ESI/MS: 315 $[M+H]^+$, 337 $[M+Na]^+$

Example 55

6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 213°C (ethanol-water)

IR (KBr): 3363, 1666, 1646, 1590, 1535, 1482, 1211 cm^{-1}

NMR (DMSO-d_6, δ): 1.24(6H, d, J=6.6 Hz), 5.11-5.24(1H, m), 6.92(1H, d, J=9.6 Hz), 7.04(2H, s), 6.96-7.08(2H, m), 7.32(1H, d, J=9.6

Hz), 7.71(1H, d, J=5.0 Hz), 8.29(1H, s)
ESI/MS: 314 $[M+H]^+$, 336 $[M+Na]^+$

Example 56

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.
mp: 203°C (ethanol-water)
IR (KBr): 3293, 1666, 1627, 1594, 1538, 1486, 1205 cm^{-1}
NMR (DMSO-d_6, δ): 0.96(6H, d, J=6.8 Hz), 2.03(3H, s), 4.90-5.04(1H, m), 6.76(1H, d, J=9.6 Hz), 7.07(2H, s), 7.10-7.29(5H, m), 8.51(1H, s)
ESI/MS: 322 $[M+H]^+$, 344 $[M+Na]^+$

Example 57

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.
mp: 198°C (ethanol-water)
IR(KBr): 3475, 1664, 1624, 1585, 1531, 1482, 1209 cm^{-1}
NMR (DMSO-d_6, δ): 1.06(6H, d, J=6.6 Hz), 2.28(3H, s), 4.98-5.12(1H, m), 6.79(1H, d, J=9.6 Hz), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.21-7.37(4H, m), 8.50(1H, s)
ESI/MS: 322 $[M+H]^+$, 344 $[M+Na]^+$

Example 58

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.
mp: 170°C (ethanol-water)

IR (KBr): 3330, 1651, 1587, 1535, 1486, 1254 cm^{-1}

NMR (DMSO-d_6, δ): 0.95(6H, d, J=6.6Hz), 3.40(3H, s), 4.90-5.03(1H, m), 6.79(1H, d, J=9.6Hz), 6.98(2H, s), 6.89-7.05(2H, m), 7.22(1H, d, J=9.6 Hz), 7.31-7.43(2H, m), 8.39(1H, s)

ESI/MS: 338 $[M+H]^+$, 360 $[M+Na]^+$

Example 59

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 211°C (ethanol-water)

IR(KBr): 3467, 1658, 1623, 1583, 1488, 1288 cm^{-1}

NMR (DMSO-d_6, δ): 1.07(6H, d, J=6.6Hz), 3.68(3H, s), 4.99-512(1H, m), 6.80(1H, d, J=9.6Hz), 6.87-6.98(3H, m), 7.09(2H, s), 7.15(1H, d, J=9.6 Hz), 7.25-7.39(1H, m), 8.50(1H, s)

ESI/MS: 338 $[M+H]^+$, 360 $[M+Na]^+$

Example 60

6-[2-Amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 259°C (ethanol-water)

IR(KBr): 3335, 1685, 1580, 1485, 1411, 1270 cm^{-1}

NMR (DMSO-d_6, δ): 3.68(3H, s), 3.78(3H, s), 6.73(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 6.95(2H, d, J=6.8 Hz), 6.99(2H, s), 7.38(2H, d, J=6.8 Hz), 8.35(1H, s)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Example 61

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-

chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 264°C (ethanol-water)
IR (KBr): 3330, 1685, 1572, 1480, 1411, 1230 cm^{-1}
NMR (DMSO-d_6, δ): 3.65(3H, s), 6.76(1H, d, J=9.6 Hz), 6.91(1H, d, J=9.6 Hz), 7.14(2H, s), 7.34-7.51(4H, m), 8.43(1H, s)
ESI/MS: 336 and 338 $[M+H]^+$

Example 62

6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 212.5°C (ethanol-water)
IR (KBr): 3330, 1666, 1580, 1485, 1411 cm^{-1}
NMR (DMSO-d_6, δ): 3.64(3H, s), 6.76(1H, d, J=9.6 Hz), 6.93(1H, d, J=9.6 Hz), 7.15(2H, s), 7.13-7.45(4H, m), 8.45(1H, s)
ESI/MS: 298 $[M+H]^+$, 320 $[M+Na]^+$

Example 63

6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 245°C (ethanol-water)
IR (KBr): 3326, 1652, 1585, 1481, 1411 cm^{-1}
NMR (DMSO-d_6, δ): 3.67(3H, s), 3.86(3H, s), 6.77(1H, d, J=9.6 Hz), 7.07(2H, s), 7.12-7.38(3H, m), 8.38(1H, s)
ESI/MS: 328 $[M+H]^+$, 350 $[M+Na]^+$

Example 64

6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according

to a similar manner to that of Example 44.

mp: 234°C (ethanol-water)

IR (KBr): 3326, 1658, 1571, 1411 cm^{-1}

NMR (DMSO-d_6, δ): 3.69(3H, s), 6.61-6.64(1H, m), 6.89(1H, d, J=9.6 Hz), 6.92-6.96(1H, m), 7.03(2H, s), 7.27(1H, d, J=9.6 Hz), 7.77-7.79(1H, m), 8.30(1H, s)

ESI/MS: 270 $[M+H]^+$, 292 $[M+Na]^+$

Example 65

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 230°C (ethanol-water)

IR (KBr): 3326, 1652, 1585, 1481, 1411cm^{-1}

NMR (DMSO-d_6, δ): 2.37(3H, s), 3.67(3H, s), 6.71(1H, d, J=9.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.05(2H, s), 7.20(2H, d, J=8.2 Hz), 7.31(2H, d, J=8.2 Hz), 8.38(1H, s)

ESI/MS: 294 $[M+H]^+$, 316 $[M+Na]^+$

Example 66

6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 231°C (ethanol-water)

IR (KBr): 3322, 1641, 1581, 1515, 1488, 1280 cm^{-1}

NMR (DMSO-d_6, δ): 3.64(3H, s), 6.78(1H, d, J=9.6 Hz), 6.98(1H, d, J=9.6 Hz), 7.15-7.19(3H, m), 7.43-7.57(2H, m), 8.45(1H, s)

ESI/MS: 316 $[M+H]^+$, 338 $[M+Na]^+$

Example 67

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-2-

methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 232°C (ethanol-water)

IR (KBr): 3386, 1629, 1575, 1481, 1263 cm^{-1}

NMR (DMSO-d_6, δ): 3.69(3H, s), 3.77(3H, s), 6.74(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 6.87-7.06(5H, m), 8.36(1H, s)

ESI/MS: 340 $[M+H]^+$, 362 $[M+Na]^+$

Example 68

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 238°C (ethanol-water)

IR (KBr): 3324, 1641, 1583, 1482, 1407 cm^{-1}

NMR (DMSO-d_6, δ): 3.64(3H, s), 6.81(1H, d, J=9.6 Hz), 7.05(1H, d, J=9.6 Hz), 7.20(2H, s), 7.23-7.29(1H, m), 7.62-7.76(2H, m), 8.46(1H, s)

ESI/MS: 370, 372 and 374 $[M+Na]^+$

Example 69

6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 270°C (ethanol-water)

IR (KBr): 3365, 1654, 1589, 1535, 1485, 1430 cm^{-1}

NMR (DMSO-d_6, δ): 3.71(3H, s), 6.92(1H, d, J=9.6 Hz), 7.03(4H, m), 7.29(1H, d, J=9.6 Hz), 7.72-7.75(1H, m), 8.27(1H, s)

ESI/MS: 286 $[M+H]^+$, 308 $[M+Na]^+$

Example 70

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 229°C (ethanol-water)

IR (KBr): 3307, 1670, 1617, 1592, 1538, 1477, 1267 cm^{-1}

NMR (DMSO-d_6, δ): 2.06(3H, s), 3.56(3H, s), 6.45(1H, d, J=9.6 Hz), 6.78(1H, d, J=9.6 Hz), 7.09(2H, s), 7.12-7.41(4H, m), 8.49(1H, s)

ESI/MS: 294 $[M+H]^+$, 316 $[M+Na]^+$

Example 71

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 214°C (ethanol-water)

IR (KBr): 3413, 1639, 1579, 1531, 1488, 1402 cm^{-1}

NMR (DMSO-d_6, δ): 2.31(3H, s), 3.67(3H, s), 6.70(1H, d, J=9.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.08(1H, s), 7.24-7.41(1H, m), 8.41(1H, s)

ESI/MS: 294 $[M+H]^+$, 316 $[M+Na]^+$

Example 72

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 225°C (ethanol-water)

IR (KBr): 3340, 1652, 1589, 1535, 1488, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 3.44(3H, s), 3.53(3H, s), 6.71(1H, d, J=9.6 Hz), 6.92(1H, d, J=9.6 Hz), 6.93-7.08(2H, m), 7.34-7.45(2H, m), 8.39(1H, s)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Example 73

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 195°C (ethanol-water)

IR (KBr): 3365, 1656, 1624, 1569, 1477, 1268 cm^{-1}

NMR (DMSO-d_6, δ): 3.66(3H, s), 3.72(3H, s), 6.72(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 6.87-7.03(2H, m), 7.10(1H, s), 7.26-7.40(2H, m), 8.41(1H, s)

ESI/MS: 310 $[M+H]^+$, 332 $[M+Na]^+$

Example 74

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: >250°C (95% EtOH)

NMR (DMSO-d_6, δ): 3.44(3H, s), 6.77(1H, d, J=9.6 Hz), 7.10(1H, d, J=9.6 Hz), 7.18(2H, brd. s), 7.32-7.47(3H, m), 7.62(1H, d, J=7.9 Hz), 8.56(1H, s)

ESI/MS: 380 and 382 $[M+Na]^+$

Example 75

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 16.

ESI/MS: 302 $[M+Na]^+$

Example 76

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-(heptadeutero-isopropyl)-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 203-204°C (95% EtOH)

NMR ($CDCl_3$, δ): 5.39(2H, brd. s), 6.73(1H, d, J=9.6 Hz), 6.93(1H, d, J=9.6 Hz), 7.22-7.41(3H, m), 7.55(1H, d, J=8.0 Hz), 8.56(1H,

s)

ESI/MS: 415 and 417 $[M+Na]^+$

Example 77

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-(heptadeuteroisopropyl)-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 16.

mp: 214-215°C (95% EtOH)

NMR (DMSO-d_6, δ): 6.80(1H, d, J=9.6 Hz), 7.18(1H, d, J=9.6 Hz), 7.30-7.41(5H, m), 8.46(1H, s)

ESI/MS: 373 $[M+Na]^+$

Example 78

A solution of 6-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone (4.00 g) and guanidine carbonate (1.00 g) in N,N-dimethylacetamide (4 ml) was stirred at 130-135°C for 2 hours. After addition of guanidine carbonate (1.00 g), the mixture was stirred at the same temperature for 8 hours and poured into water (80 ml) to give a precipitate. The precipitate was collected by filtration, dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was dissolved in acetone under reflux and diisopropyl ether was added to the solution to give 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.26 g).

mp: 221-222°C (chloroform - diisopropyl ether)

IR (KBr): 3500, 3286, 3151, 1658, 1620, 1587, 1539 cm^{-1}

ESI/MS: 729$[2M+Na]^+$, 376$[M+Na]^+$, 354$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.26(6H, d, J=6.66 Hz), 2.50(3H, s), 5.20(2H, br.s), 5.29(1H, 7-plet, J=6.66 Hz), 6.70(1H, d, J=9.50 Hz), 6.82(1H, d, J=9.50 Hz), 7.24-7.35(5H, m)

^1H NMR (DMSO-d_6, δ): 1.09(6H, d, J=6.62 Hz), 2.47(3H, s), 5.08(1H, 7-plet, J=6.62 Hz), 6.78(1H, d, J=9.52 Hz), 7.03(2H, br.s), 7.15(1H, d, J=9.52 Hz), 7.23-7.35(5H, m)

Elemental Analysis for $C_{18}H_{19}N_5OS$
Calcd.: C,61.17; H,5.42; N,19.81
Found : C,61.27; H,5.53; N,19.71

Example 79

Under ice-cooling, 3-chloroperbenzoic acid (70 % purity) (0.70 g) was added to a solution of 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (1.01 g) in dichloromethane (10 ml). After stirring at ambient temperature for 5 hours, the mixture was washed with saturated aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel. With an elution of a mixture of n-hexane and ethyl acetate (30 : 70 v/v) was given 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (29 mg). Next, with an elution of a mixture of methanol and ethyl acetate (2 : 98 v/v) was given 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.00 g).

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 225-227°C (dimethyl sulfoxide - acetone)
IR (KBr): 3408, 3302, 3207, 1658, 1630, 1591, 1560, 1512 cm^{-1}
ESI/MS: 761$[2M+Na]^+$, 392$[M+Na]^+$
ESI/MS-Neg: 368$[M-H]^-$
^1H NMR ($CDCl_3$, δ): 1.36(3H, d, J=6.60 Hz), 1.39(3H, d, J=6.60 Hz), 2.99(3H, s), 5.39(1H, 7-plet, J=6.60 Hz), 5.83(2H, br.s), 6.59(1H, d, J=9.56 Hz), 6.64(1H, d, J=9.56 Hz), 7.31-7.48(5H, m)
Elemental Analysis for $C_{18}H_{19}N_5O_2S \cdot 0.2H_2O$

Calcd.: C,57.96; H,5.24; N,18.77
Found : C,58.18; H,5.17; N,18.72

6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 210-211°C (ethanol)
IR (KBr): 3384, 3203, 1653, 1631, 1587, 1564, 1512 cm^{-1}
ESI/MS-Neg: 384 $[M-H]^-$
^1H NMR ($CDCl_3$, δ): 1.21(6H, d, J=6.62 Hz), 3.28(3H, s), 5.27(1H, 7-plet, J=6.62 Hz), 5.54(2H, br.s), 6.74(1H, d, J=9.52 Hz), 6.96(1H, d, J=9.52 Hz), 7.28-7.38(5H, m)
Elemental Analysis for $C_{18}H_{19}N_5O_3S \cdot 0.2H_2O$
Calcd.: C,55.57; H,5.03; N,18.00
Found : C,55.73; H,5.05; N,17.71

Example 80

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and sodium methoxide (35 mg) in methanol (0.6 ml) was heated under reflux for 5 hours. After concentration of the mixture, a residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 20 : 80 v/v) to give 6-(2-amino-4-methoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (107 mg).

mp: 230-233°C (ethanol)
IR (KBr): 3519, 3394, 1660, 1606, 1581, 1543 cm^{-1}
ESI/MS: 697 $[2M+Na]^+$, 360 $[M+Na]^+$, 338 $[M+H]^+$
^1H NMR ($CDCl_3$, δ): 0.92(6H, d, J=6.62 Hz), 3.95(3H, s), 5.11(1H, 7-plet, J=6.62 Hz), 5.22(2H, br.s), 6.84(1H, d, J=9.52 Hz), 7.21-7.30(6H, m)
Elemental Analysis for $C_{18}H_{19}N_5O_2$
Calcd.: C,64.08; H,5.68; N,20.76

Found : C,64.24; H,5.64; N,20.75

Example 81

Sodium hydride (60 % in oil suspension) (19.5 mg) was added in ethanol (0.6 ml) under ice-cooling. After stirring at the ambient temperature for 30 minutes, 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture. The mixture was heated at 100-105°C for 5 hours in a sealed tube. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-(2-amino-4-ethoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (99 mg).

mp: 187.5-188.5°C (ethanol - diisopropyl ether)

IR (KBr): 3521, 3388, 1658, 1608, 1579, 1545 cm^{-1}

ESI/MS: 725$[2M+Na]^+$, 374$[M+Na]^+$, 352$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.94(6H, d, J=6.62 Hz), 1.35(3H, t, J=7.06 Hz), 4.41(2H, q, J=7.06 Hz), 5.05-5.19(3H, m), 6.82(1H, d, J=9.50 Hz), 7.21(1H, d, J=9.50 Hz), 7.22-7.30(5H, m)

Elemental Analysis for $C_{19}H_{21}N_5O_2 \cdot 0.1H_2O$

Calcd.: C,64.61; H,6.05; N,19.83

Found : C,64.60; H,5.93; N,19.81

Example 82

6-(2-Amino-4-isopropoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-propanol according to a similar manner to that of Example 81.

mp: 176.5-177.5°C (diisopropyl ether)

IR (KBr): 3352, 3307, 3184, 1664, 1647, 1635, 1572, 1545 cm^{-1}

ESI/MS: 753$[2M+Na]^+$, 388$[M+Na]^+$, 366$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.95(6H, d, J=6.72 Hz), 1.32(6H, d, J=6.25

Hz), 5.07-5.19(3H, m), 5.40(1H, 7-plet, J=6.25 Hz), 6.81(1H, d, J=9.52 Hz), 7.17(1H, d, J=9.52 Hz), 9.26(5H, s)

Example 83

6-[2-Amino-4-(cyclobutyloxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and cyclobutanol according to a similar manner to that of Example 81.

mp: 161-162.5°C (acetone - n-hexane)

IR (KBr): 3381, 3325, 3155, 1653, 1589, 1572, 1547 cm^{-1}

ESI/MS: 400$[M+Na]^+$, 378$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.94(6H, d, J=6.60 Hz), 1.62-1.85(2H, m), 2.02-2.18(2H, m), 2.39-2.50(2H, m), 5.05-5.33(4H, m), 6.82(1H, d, J=9.52 Hz), 7.19-7.30(6H, m)

Elemental Analysis for $C_{21}H_{23}N_5O_2$

Calcd.: C,66.83; H,6.14; N,18.55

Found : C,66.98; H,6.17; N,18.60

Example 84

6-[4-(Allyloxy)-2-amino-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-propen-1-ol according to a similar manner to that of Example 81.

mp: 130.5-132.5°C (diisopropyl ether)

IR (KBr): 3489, 3311, 3192, 1647, 1626, 1576, 1545 cm^{-1}

ESI/MS: 749$[2M+Na]^+$, 386$[M+Na]^+$, 364$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.94(6H, d, J=6.56 Hz), 4.85-4.90(2H, m), 5.06-5.36(5H, m), 5.91-6.10(1H, m), 6.83(1H, d, J=9.52 Hz), 7.23(1H, d, J=9.52 Hz), 7.27(5H, s)

Example 85

Sodium hydride (60 % in oil suspension) (19.5 mg) was added in 2-propyn-1-ol (0.6 ml) under ice-cooling. After stirring at the ambient temperature for 30 minutes,

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture. The mixture was heated at 100-105°C for 5 hours. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-[2-amino-4-phenyl-6-(2-propynyloxy)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (101 mg).

mp: 145-146.6°C (acetone - diisopropyl ether)

IR (KBr): 3410, 3294, 3176, 2121, 1657, 1637, 1591, 1574, 1545 cm^{-1}

ESI/MS: 745[2M+Na]$^+$, 384[M+Na]$^+$, 362[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 0.93(6H, d, J=6.60 Hz), 2.49(1H, t, J=2.35 Hz), 5.00(2H, d, J=2.35 Hz), 5.09(1H, 7-plet, J=6.60 Hz), 5.20(2H, br.s), 6.84(1H, d, J=9.52 Hz), 7.24(1H, d, J=9.52 Hz), 7.27(5H, s)

Elemental Analysis for $C_{20}H_{19}N_5O_2 \cdot 0.1H_2O$

Calcd.: C,66.14; H,5.33; N,19.28

Found : C,66.19; H,5.25; N,19.19

Example 86

6-[2-Amino-4-(2-hydroxyethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and ethylene glycol according to a similar manner to that of Example 85.

mp: 182-183°C (ethanol)

IR (KBr): 3352, 3178, 1646, 1579, 1546 cm^{-1}

ESI/MS: 757[2M+Na]$^+$, 390[M+Na]$^+$, 368[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.76(6H, d, J=6.60 Hz), 3.63-3.72(2H, m), 4.36(2H, t, J=5.04 Hz), 4.81(1H, t, J=5.22 Hz), 4.87(1H, 7-plet, J=6.60 Hz), 6.85(1H, d, J=9.54 Hz), 6.95(2H, br.s), 7.16-7.34(5H, m), 7.55(1H, d, J=9.54 Hz)

Elemental Analysis for $C_{19}H_{21}N_5O_3$

Calcd.: C,62.11; H,5.76; N,19.06

Found : C,62.19; H,5.78; N,18.98

Example 87

6-[2-Amino-4-(2-methoxyethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-methoxyethanol according to a similar manner to that of Example 85.

mp: 128-130°C (ethanol)

IR (KBr): 3475, 3325, 3215, 1647, 1630, 1576, 1547 cm^{-1}

ESI/MS: 785$[2M+Na]^+$, 404$[M+Na]^+$, 382$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.93(6H, d, J=6.60 Hz), 3.37(3H, s), 3.65-3.71(2H, m), 4.48-4.54(2H, m), 5.02-5.19(3H, m), 6.82(1H, d, J=9.52 Hz), 7.24-7.31(6H, m)

Example 88

6-{2-Amino-4-[2-(dimethylamino)ethoxy]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-(dimethylamino)ethanol according to a similar manner to that of Example 85.

mp: 130-131.5°C (acetone - diisopropyl ether)

IR (KBr): 3365, 3172, 1664, 1649, 1589, 1570, 1550 cm^{-1}

ESI/MS: 811$[2M+Na]^+$, 417$[M+Na]^+$, 395$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.93(6H, d, J=6.62 Hz), 2.27(6H, s), 2.66(2H, t, J=5.95 Hz), 4.47(2H, t, J=5.95 Hz), 5.11(1H, 7-plet, J=6.62 Hz), 5.18(2H, br.s), 6.82(1H, d, J=9.52 Hz), 7.24-7.30(6H, m)

Example 89

Sodium hydride (60 % in oil suspension) (19.5 mg) was added to a solution of methyl hydroxyacetate (40.7 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfinyl)-

6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixtutre and the mixture was heated at 100-105°C for 7 hours. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give methyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate as an amorphous (120 mg).

mp: 150-152.5°C

IR (KBr): 3419, 3386, 3309, 3197, 1761, 1657, 1635, 1591, 1545 cm^{-1}

ESI/MS: 813$[M+Na]^+$, 418$[M+Na]^+$, 396$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.89(6H, d, J=6.60 Hz), 3.80(3H, s), 4.94(2H, s), 5.10(1H, 7-plet, J=6.60 Hz), 5.24(2H, br.s), 6.86(1H, d, J=9.52 Hz), 7.27(5H, s), 7.43(1H, d, J=9.52 Hz)

Elemental Analysis for $C_{20}H_{21}N_5O_4 \cdot 0.3H_2O$

Calcd.: C,59.93; H,5.43; N,17.47

Found : C,60.13; H,5.39; N,17.26

Example 90

2-(2-{[2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}-ethyl)-1H-isoindole-1,3(2H)-dione was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-(2-hydroxyethyl)-1H-isoindole-1,3(2H)-dione according to a similar manner to that of Example 89.

mp: 231.5-232.5°C (acetone - diisopropyl ether)

IR (KBr): 3313, 3195, 1774, 1716, 1653, 1622, 1577, 1545 cm^{-1}

ESI/MS: 1015$[2M+N]^+$, 519$[M+N]^+$, 497$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.83(6H, d, J=6.62 Hz), 4.07(2H, t, J=5.35 Hz), 4.66(2H, t, J=5.35 Hz), 4.93-5.10(3H, m), 6.71(1H, d, J=9.50 Hz), 7.18-7.27(6H, m), 7.69-7.84(4H, m)

Elemental Analysis for $C_{27}H_{24}N_6O_4 \cdot 0.1H_2O$

Calcd.: C,65.08; H,4.89; N,16.86

Found : C,64.98; H,4.91; N,16.78

Example 91

Sodium hydride (60 % in oil suspension) (19.5 mg) was added in 1-propanol (0.6 ml) under ice-cooling. After stirring at the ambient temperature for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (156.5 mg) was added to the mixture. The mixture was heated at 100-105°C for 7 hours in a sealed tube. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 20 : 80 v/v) to give 6-(2-amino-4-phenyl-6-propoxy-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (136 mg).

mp: 127.5-129°C (ethanol - diisopropyl ether)

IR (KBr): 3354, 3311, 1662, 1589, 1570, 1547 cm^{-1}

ESI/MS: 388$[M+Na]^+$, 366$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.92-1.00(9H, m), 1.65-1.83(2H, m), 4.30(2H, t, J=6.55 Hz), 5.05-5.19(3H, m), 6.82(1H, d, J=9.52 Hz), 7.21(1H, d, J=9.52 Hz), 7.26(5H, s)

Example 92

6-[2-Amino-4-(2-fluoroethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-fluoroethanol according to a similar manner to that of Example 91.

mp: 129-130.5°C (ethanol - diisopropyl ether)

IR (KBr): 3491, 3327, 3207, 1649, 1635, 1576, 1545 cm^{-1}

ESI/MS: 761$[2M+Na]^+$, 392$[M+Na]^+$, 370$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.93(6H, d, J=6.60 Hz), 4.54-4.58(2H, m), 4.66-4.72(1H, m), 4.79-4.84(1H, m), 5.06-5.20(3H, m), 6.83(1H, d, J=9.52 Hz), 7.21-7.28(6H, m)

Example 93

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of benzyl alcohol (52.4 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixtutre and the mixture was heated at 100-105°C for 7 hours. Water (4.5 ml) was added to the mixture to give a solid. The solid was collected by filtration, dissolved in chloroform (5 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give 6-[2-amino-4-(benzyloxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (124 mg).

mp: 162-163°C (acetone)

IR (KBr): 3357, 3309, 3168, 1651, 1589, 1570, 1545, 1490 cm^{-1}

ESI/MS: 849$[2M+Na]^+$, 436$[M+Na]^+$, 414$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.93(6H, d, J=6.61 Hz), 5.11(1H, 7-plet, J=6.61 Hz), 5.17(2H, s), 5.43(2H, s), 6.79(1H, d, J=9.52 Hz), 7.18(1H, d, J=9.52 Hz), 7.23-7.39(10H, m)

Elemental Analysis for $C_{24}H_{23}N_5O_2 \cdot 0.1H_2O$

Calcd.: C,69.41; H,5.63; N,16.86

Found : C,69.26; H,5.59; N,16.91

Example 94

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of 2-pyridinylmethanol (48.8 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixtutre and the mixture was heated at 100-105°C for 7 hours. Water (4.5 ml) was added to the mixture to give a solid. The solid was collected by filtration, dissolved

in chloroform (5 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-[2-amino-4-phenyl-6-(2-pyridinylmethoxy)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (51 mg).

mp: 177-178°C (acetone - diisopropyl ether)

IR (KBr): 3491, 3141, 1658, 1631, 1591, 1554 cm^{-1}

ESI/MS: 851$[2M+Na]^+$, 437$[M+Na]^+$, 415$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.81(6H, d, J=6.62 Hz), 4.93(1H, 7-plet, J=6.62 Hz), 5.49(2H, s), 6.86(1H, d, J=9.52 Hz), 7.02(2H, s), 7.21-7.42(7H, m), 7.54(1H, d, J=9.52 Hz), 7.77-7.86(1H, m), 8.54-8.57(1H, m)

Example 95

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of 2-(2-pyridinyl)ethanol (57 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture and the mixture was heated at 100-105°C for 7 hours. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (methanol - ethyl acetate 1 : 99 v/v) to give 6-{2-Amino-4-phenyl-6-[2-(2-pyridinyl)ethoxy]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared as a syrup (71 mg).

IR (KBr): 3471-3327, 3201, 1651, 1589, 1572, 1545 cm^{-1}

ESI/MS: 879$[2M+Na]^+$, 451$[M+Na]^+$, 429$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.88(6H, d, J=6.62 Hz), 3.20(2H, t, J=6.47 Hz), 4.77(2H, t, J=6.47 Hz), 5.02-5.13(3H, m), 6.67(1H, d, J=9.52 Hz), 6.91(1H, d, J=9.52 Hz), 7.11-7.32(7H, m), 7.53-7.62(1H, m), 8.54-8.57(1H, m)

Example 96

6-[2-Amino-4-(cyclohexyloxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and cyclohexanol according to a similar manner to that of Example 94.

mp: 173-175°C (diisopropyl ether)

IR (KBr): 3419-3309, 3182, 1653, 1589, 1570, 1545 cm^{-1}

ESI/MS: 833$[2M+Na]^+$, 428$[M+Na]^+$, 406$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.84-1.61(8H, m), 0.94(6H, d, J=6.62 Hz), 1.87-1.95(2H, m), 5.05-5.22(4H, m), 6.82(1H, d, J=9.52 Hz), 7.21(1H, d, J=9.52 Hz), 7.23-7.31(5H, m)

Example 97

6-[2-Amino-4-phenyl-6-(tetrahydro-2H-pyran-4-yloxy)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and tetrahydro-2H-pyran-4-ol according to a similar manner to that of Example 94.

mp: 207-209°C (ethanol - diisopropyl ether)

IR (KBr): 3373, 3329, 3211, 1670, 1649, 1589, 1572, 1539 cm^{-1}

ESI/MS: 837$[2M+Na]^+$, 430$[M+Na]^+$, 408$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.97(6H, d, J=6.60 Hz), 1.65-1.85(2H, m), 1.99-2.09(2H, m), 3.54-3.67(2H, m), 3.79-3.91(2H, m), 5.07-5.21(3H, m), 5.29-5.40(1H, m), 6.82(1H, d, J=9.52 Hz), 7.18(1H, d, J=9.52 Hz), 7.25-7.27(5H, m)

Elemental Analysis for $C_{22}H_{25}N_5O_3$

Calcd.: C,64.85; H,6.18; N,17.19

Found : C,65.05; H,6.20; N,17.20

Example 98

6-(2-Amino-4-phenoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and phenol according to a similar manner to that of Example 94.

mp: 218-221°C (methanol)

IR (KBr): 3394, 3305, 3190, 1666, 1631, 1593, 1572, 1539 cm^{-1}

ESI/MS: 821[2M+Na]$^+$, 422[M+Na]$^+$, 400[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.83(6H, d, J=6.60 Hz), 4.94(1H, 7-plet, J=6.60Hz), 6.89(1H, d, J=9.54Hz), 6.99(2H, br.s), 7.20-7.48(10H, m), 7.68(1H, d, J=9.54 Hz)

Elemental Analysis for $C_{23}H_{21}N_5O_2 \cdot 3H_2O$

Calcd.: C,68.23; H,5.38; N,17.30

Found : C,68.09; H,5.22; N,17.24

Example 99

Potassium tert-butoxide (30 mg) was added to a mixture of methyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate (150 mg) in formamide (1.5 ml) and the mixture was heated at 100-105°C for 3 hours. Water (9 ml) was added to give 2-{[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetamide as a solid (101 mg).

mp: 257-261°C (formamide - water)

IR (KBr): 3475, 3411, 3205, 1678, 1637, 1593, 1545 cm^{-1}

ESI/MS: 783[2M+Na]$^+$, 403[M+Na]$^+$, 381[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.75(6H, d, J=6.61 Hz), 4.77(2H, s), 4.90(1H, 7-plet, J=6.61 Hz), 6.89(1H, d, J=9.56 Hz), 6.96(2H, s), 7.04-7.39(7H, m), 7.69(1H, d, J=9.56 Hz)

Elemental Analysis for $C_{19}H_{20}N_6O_3$

Calcd.: C,59.99; H,5.30; N,22.09

Found : C,59.95; H,5.27; N,22.06

Example 100

A solution of methyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate (600 mg) in a mixture of 1N aqueous sodium hydroxide (4.5 ml) and tetrahydrofuran (4.5 ml) was heated at 60-65°C for 3 hours. Under ice-cooling, 1N

hydrochloric acid (4.5 ml) was added to the mixture. The mixture was extracted with ethyl acetate, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was suspended with acetone to give {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid as a solid (406 mg).

mp: 215-217°C (acetone)

IR (KBr): 1653, 1591, 1576 cm^{-1}

ESI/MS: 404$[M+Na]^+$, 382$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.76(6H, d, J=6.60 Hz), 4.83-4.98(3H, m), 6.90(1H, d, J=9.53 Hz), 7.00(2H, s), 7.19-7.37(5H, m), 7.54(1H, d, J=9.53 Hz), 13.2(1H, br.s)

Example 101

A mixture of {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid (150 mg), methylamine hydrochloride (31.9 mg), 1-hydroxybenzotriazole (63.8 mg), triethylamine (65.8 μl) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (90.5 mg) in dimethylformamide (0.9 ml) was stirred at ambient temperature for 70 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure and purified by column chromatography on silica gel (methanol - ethyl acetate 2 : 98 v/v) to give 2-{[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}-N-methylacetamide as a solid (142 mg).

mp: 204-205.5°C (ethanol - diisopropyl ether)

IR (KBr): 3440, 3307, 3168, 1680, 1658, 1595, 1539 cm^{-1}

ESI/MS-Neg: 393$[M-H]^-$

^1H NMR ($CDCl_3$, δ): 1.00(6H, d, J=6.62 Hz), 2.87(3H, d, J=4.94

Hz), 4.89(2H, s), 5.15-5.31(3H, m), 6.10(1H, br.s), 6.81(1H, d, J=9.50 Hz), 7.04(1H, d, J=9.50 Hz), 7.26-7.35(5H, m)

Elemental Analysis for $C_{20}H_{22}N_6O_3$

Calcd.: C,60.90; H,5.62; N,21.31

Found : C,60.82; H,5.64; N,21.22

Example 102

2-{[2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}-N,N-dimethylacetamide was prepared from {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid and N,N-dimethylamine hydrochloride according to a similar manner to that of Example 101.

mp: 133-135.5°C (acetone - hexane)

IR (KBr): 3462, 3309, 3192, 1657, 1591, 5174, 1545 cm^{-1}

ESI/MS: 839$[2M+Na]^+$, 431$[M+Na]^+$, 409$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.87(6H, d, J=6.62 Hz), 3.01(3H, s, J=3.01 Hz), 3.04(3H, s, J=3.04 Hz), 5.00-5.14(5H, m), 6.86(1H, d, J=9.52 Hz), 7.21-7.30(5H, m), 7.67(1H, d, J=9.52 Hz)

Example 103

2-{[2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}-N-cyclopropylacetamide was prepared from {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid and cyclopropylamine according to a similar manner to that of Example 101.

mp: 87-92°C (amorphous)

IR (KBr): 3316, 1651, 1589, 1576, 1541 cm^{-1}

ESI/MS: 863$[2M+Na]^+$, 443$[M+Na]^+$, 421$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.41-0.50(2H, m), 0.75-0.90(2H, m), 1.06(6H, d, J=6.60 Hz), 2.64-2.75(1H, m), 4.84(2H, s), 5.21(1H, 7-plet, J=6.60 Hz), 5.29(2H, s), 6.15(1H, br.s), 6.82(1H, d, J=9.52 Hz), 7.09(1H, d, J=9.52 Hz), 7.26-7.34(5H, m)

Example 104

A solution of 2-(2-{[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}ethyl)-1H-isoindole-1,3(2H)-dione (225 mg) and hydrazine hydrate (0.5 ml) in ethanol (4.5 ml) was heated under reflux for 3 hours. The precipitate was filtered off and the mother liquid was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (Chromatorex NH) (methanol - ethyl acetate 1: 99 v/v) to give 6-[2-amino-4-(2-aminoethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (108 mg).

mp: 213-216°C (acetone)

IR (KBr): 3431, 3352, 3248, 1666, 1647, 1564 cm^{-1}

ESI/MS: 755[2M+Na]$^+$, 389[M+Na]$^+$, 367[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.41(6H, d, J=6.62 Hz), 3.60-3.72(2H, m), 3.78-3.87(2H, m), 5.05(2H, br.s), 5.35(1H, 7-plet, J=6.62 Hz), 6.47(1H, d, J=9.60 Hz), 6.50(1H, d, J=9.60 Hz), 7.26-7.42(7H, m)

Elemental Analysis for $C_{19}H_{22}N_6O_2 \cdot 0.4H_2O$

Calcd.: C,61.08; H,6.15; N,22.49

Found : C,61.21; H,6.23; N,22.32

Example 105

In a sealed tube, a mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (200 mg) in 2M ammonia solution in methanol (2 ml) was heated at 60-65°C for 90 hours. After cooling at ambient temperature, the precipitate was removed by filtration and the mother liquid was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol - ethyl acetate 3 : 97 v/v) to give 6-(2,4-diamino-6-phenyl-5-pyrimidinyl)-

2-isopropyl-3(2H)-pyridazinone as a solid (20 mg).
mp: 258-260°C (ethanol suspension)
IR (KBr): 3417, 3363, 1645, 1610, 1576, 1552 cm^{-1}
ESI/MS: 345$[M+Na]^+$, 323$[M+H]^+$
^1H NMR (DMSO-d_6, δ): 1.01(6H, d, J=6.60 Hz), 5.05(1H, 7-plet, J=6.60 Hz), 6.27(2H, br.s), 6.34(2H, br.s), 6.68(1H, d, J=9.50 Hz), 6.93(1H, d, J=9.50 Hz), 7.18-7.30(5H, m)

Example 106

6-[2-Amino-4-(methylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 40 % methylamine solution in methanol according to a similar manner to that of Example 105.
mp: 268-270°C (methanol)
IR (KBr): 3357, 3165, 1657, 1587, 1564 cm^{-1}
ESI/MS: 695$[2M+Na]^+$, 359$[M+Na]^+$, 337$[M+H]^+$
^1H NMR (DMSO-d_6, δ): 1.09(6H, d, J=6.61 Hz), 2.80(3H, d, J=4.60 Hz), 5.04(1H, 7-plet, J=6.61 Hz), 6.34(2H, br.s), 6.47(1H, q, J=4.60 Hz), 6.71(1H, d, J=9.50 Hz), 6.99(1H, d, J=9.50 Hz), 7.16-7.28(5H, m).
Elemental Analysis for $C_{18}H_{20}N_6O$
Calcd.: C,64.27; H,5.99; N,24.98
Found : C,64.21; H,6.00; N,24.85

Example 107

6-[2-Amino-4-(dimethylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2M dimethylamine solution in tetrahydrofuran according to a similar manner to that of Example 105.
mp: 293-296°C (tetrahydrofuran)
IR (KBr): 3494, 3275, 3136, 1658, 1622, 1587, 1558 cm^{-1}

ESI/MS: 723[2M+Na]$^+$, 373[M+Na]$^+$, 351[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 1.01(6H, d, J=6.60 Hz), 2.78(6H, s), 5.03(1H, 7-plet, J=6.60 Hz), 6.39(2H, br.s), 6.70(1H, d, J=9.50 Hz), 7.05-7.26(6H, m)

Elemental Analysis for $C_{19}H_{22}N_6O$

Calcd.: C,65.12; H,6.33; N,23.98

Found : C,65.07; H,6.39; N,23.93

Example 108

6-[2-Amino-4-(ethylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2M ethylamine solution in tetrahydrofuran according to a similar manner to that of Example 105.

mp: 208-209°C (ethanol - diisopropyl ether)

IR (KBr): 3354, 3305, 3180, 1657, 1635, 1587, 1560 cm^{-1}

ESI/MS: 373[M+Na]$^+$, 351[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.25(3H, t, J=5.49 Hz), 1.43(6H, d, J=6.62 Hz), 3.43-3.57(2H, m), 4.98(2H, br.s), 5.38(1H, 7-plet, J=6.62 Hz), 6.46(1H, d, J=9.91 Hz), 6.48(1H, d, J=9.91 Hz), 6.83(1H, br.s), 7.26-7.41(5H, m)

Elemental Analysis for $C_{19}H_{22}N_6O$

Calcd.: C,65.12; H,6.33; N,23.98

Found : C,64.94; H,6.44; N,23.73

Example 109

6-[2-Amino-4-phenyl-6-(propylamino)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and propylamine according to a similar manner to that of Example 105.

mp: 209-212°C (propylamine)

IR (KBr): 3344, 3305, 3134, 1655, 1624, 1587, 1566 cm^{-1}

ESI/MS: 751[2M+Na]$^+$, 387[M+Na]$^+$, 365[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.88(3H, t, J=7.35 Hz), 1.16(6H, d, J=6.60 Hz), 1.42-1.61(2H, m), 3.24-3.34(2H, m), 5.08(1H, 7-plet, J=6.60 Hz), 6.32(2H, br.s), 6.55(1H, t, J=5.49 Hz), 6.66(1H, d, J=9.52 Hz), 6.84(1H, d, J=9.52 Hz), 7.18-7.30(5H, m)

Elemental Analysis for $C_{20}H_{24}N_6O \cdot 0.1H_2O$:

Calcd.: C,65.59; H,6.66; N,22.95

Found : C,65.57; H,6.96; N,22.97

Example 110

6-[2-Amino-4-(isopropylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and isopropylamine according to a similar manner to that of Example 105.

mp: 234-236°C (methanol)

IR (KBr): 3340, 3280, 3144, 1657, 16226, 1587, 1562 cm^{-1}

ESI/MS: 751[2M+Na]$^+$, 387[M+Na]$^+$, 365[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.50 Hz), 1.22(6H, d, J=6.60 Hz), 4.26-4.36(1H, m), 5.12(1H, 7-plet, J=6.60 Hz), 6.35(2H, br.s), 6.41(1H, d, J=7.78 Hz), 6.60(1H, d, J=9.56 Hz), 6.72(1H, d, J=9.56 Hz), 7.19-7.32(5H, m)

Elemental Analysis for $C_{20}H_{24}N_6O$

Calcd.: C,65.91; H,6.64; N,23.06

Found : C,65.83; H,6.90; N,22.97

Example 111

6-[4-(Allylamino)-2-amino-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and allylamine according to a similar manner to that of Example 105.

mp: 191.5-192.5°C (ethanol - diisopropyl ether)

IR (KBr): 3345, 3180, 1668, 1649, 1595, 1570, 1547 cm^{-1}

ESI/MS: 385[M+Na]$^+$, 363[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.39(6H, d, J=6.68 Hz), 4.09-4.16(2H, m), 5.01(2H, br.s), 5.15-5.40(3H, m), 5.85-6.10(1H, m), 6.48(2H, s), 6.95(1H, br.s), 7.26-7.41(5H, m)

Elemental Analysis for $C_{20}H_{22}N_6O$

Calcd.: C,66.28; H,6.12; N,23.19

Found : C,66.11; H,6.26; N,23.13

Example 112

6-[2-Amino-4-(cyclopropylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and cyclopropylamine according to a similar manner to that of Example 105.

mp: 237-239°C (methanol)

IR (KBr): 3325, 3155, 1655, 1624, 1587, 1562 cm^{-1}

ESI/MS: 747$[2M+Na]^+$, 385$[M+Na]^+$, 363$[M+H]^+$

^{1}H NMR (DMSO-d_6, δ): 0.42-0.51(2H, m), 0.63-0.73(2H, m), 1.12(6H, d, J=6.60 Hz), 2.78-2.91(1H, m), 5.06(1H, 7-plet, J=6.60 Hz), 6.39(2H, br.s), 6.60-6.66(2H, m), 6.82(1H, d, J=9.52 Hz), 7.16-7.30(5H, m)

Elemental Analysis for $C_{20}H_{22}N_6O$

Calcd.: C,66.28; H,6.12; N,23.19

Found : C,66.39; H,6.25; N,23.13

Example 113

6-[2-Amino-4-(tert-butylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and tert-butylamine according to a similar manner to that of Example 105.

mp: 202-204°C (ethanol - diisopropyl ether)

IR (KBr): 3502, 3284, 3120, 1668, 1630, 1593, 1566 cm^{-1}

ESI/MS: 401$[M+Na]^+$, 379$[M+H]^+$

^{1}H NMR ($CDCl_3$, δ): 1.42(6H, d, J=6.62 Hz), 1.49(9H, s), 4.88(2H,

br.s), 5.36(1H, 7-plet, J=6.62 Hz), 6.46(2H, s), 6.58(1H, br.s), 7.26-7.37(5H, m)

Elemental Analysis for $C_{21}H_{26}N_6O$

Calcd.: C,66.64; H,6.92; N,22.20

Found : C,66.88; H,7.10; N,22.21

Example 114

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) in 2-aminoethanol (2 ml) was heated at 100-105°C for 10 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give 6-{2-amino-4-[(2-hydroxyethyl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (96 mg).

mp: 221.5-223.5°C (ethanol)

IR (KBr): 3431, 3352, 3248, 1666, 1647, 1564 cm^{-1}

ESI/MS: 389$[M+Na]^+$, 367$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.69(6H, d, J=6.60 Hz), 3.35-3.51(4H, m), 4.73(1H, br.s), 5.08(1H, 7-plet, J=6.60 Hz), 6.38(2H, br.s), 6.64(1H, d, J=9.54 Hz), 6.79(1H, t, J=5.28 Hz), 6.82(1H, d, J=9.54 Hz), 7.20-7.32(5H, m)

Elemental Analysis for $C_{19}H_{22}N_6O_2 \cdot 0.5H_2O$

Calcd.: C,60.79; H,6.17; N,22.39

Found : C,60.60; H,6.31; N,22.21

Example 115

In a sealed tube, a mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) in 2-methoxyethylamine (2 ml) was heated at 100-105°C for 10 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 6-{2-amino-4-[(2-methoxyethyl)amino]-6-

phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (88 mg).

mp: 168-170°C (ethanol - diisopropyl ether)

IR (KBr): 3357, 3172, 1662, 1639, 1589, 1558 cm^{-1}

ESI/MS: 783$[2M+Na]^+$, 403$[M+Na]^+$, 381$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.43(6H, d, J=6.64 Hz), 3.36(3H, s), 3.56(2H, t, J=4.78 Hz), 3.65-3.74(2H, m), 4.98(2H, br.s), 5.36(1H, 7-plet, J=6.64 Hz), 6.45(1H, d, J=9.93 Hz), 6.49(1H, d, J=9.63 Hz), 7.12(1H, t, J=4.98 Hz), 7.26-7.40(5H, m)

Elemental Analysis for $C_{20}H_{24}N_6O_2$

Calcd.: C,63.14; H,6.36; N,22.09

Found : C,63.28; H,6.56; N,21.87

Example 116

6-{2-Amino-4-[(2-aminoethyl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and ethylenediamine according to a similar manner to that of Example 114.

mp: 194-197°C (diisopropyl ether)

IR (KBr): 3345, 3172, 1653, 1585, 1558 cm^{-1}

ESI/MS: 388$[M+Na]^+$, 366$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.43(6H, d, J=6.61 Hz), 1.4-1.7(2H, m), 2.94(2H, t, J=6.03 Hz), 3.50-3.65(2H, m), 4.97(2H, br.s), 5.36(1H, 7-plet, J=6.61 Hz), 6.49(2H, s), 7.07(1H, t, J=5.08 Hz), 7.26-7.39(5H, m)

Example 117

6-(2-Amino-4-{[2-(dimethylamino)ethyl]amino}-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and N,N-dimethylethylenediamine according to a similar manner to that of Example 115.

mp: 164-165.5°C (ethanol - diisopropyl ether)

IR (KBr): 3375, 3321, 3211, 1666, 1641, 1593, 1547 cm^{-1}

ESI/MS: 809$[2M+Na]^+$, 416$[M+Na]^+$, 394$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.44(6H, d, J=6.63 Hz), 2.20(6H, s), 2.49(2H, t, J=5.99Hz), 3.49-3.59(2H, m), 5.05(2H, br.s), 5.33(1H, 7-plet, J=6.63 Hz), 6.48(2H, s), 6.99(1H, t, J=4.34 Hz), 7.25-7.38(5H, m)

Elemental Analysis for $C_{21}H_{27}N_7O$

Calcd.: C,64.10; H,6.92; N,24.92

Found : C,64.13; H,7.02; N,24.91

Example 118

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg), 2-aminoacetamide hydrochloride (89.8 mg) and N-ethyl-N,N-diisopropylamine (0.141 ml) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was crystallized from a mixture of ethanol and diisopropyl ether to give 2-{[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]amino}acetamide as a solid (77 mg).

mp: 235-237.5°C (ethanol - diisopropyl ether)

IR (KBr): 3338, 3207, 16535, 1585, 1558 cm^{-1}

ESI/MS: 781$[2M+Na]^+$, 402$[M+Na]^+$, 380$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 1.17(6H, d, J=6.61 Hz), 3.90(2H, d, J=5.00 Hz), 5.06(1H, 7-plet, J=6.61 Hz), 6.41(2H, br.s), 6.68(1H, d, J=9.54 Hz), 6.84(1H, t, J=5.00 Hz), 6.96(1H, d, J=9.54 Hz), 7.13(1H, br.s), 7.20-7.32(5H, m), 7.38(1H, br.s)

Elemental Analysis for $C_{19}H_{21}N_7O_2 \cdot 0.3H_2O$

Calcd.: C,59.30; H,5.66; N,25.48

Found : C,59.54; H,5.60; N,25.23

Example 119

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-

5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and benzylamine (88.7 μl) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was crystallized from a mixture of ethanol and diisopropyl ether to give 6-[2-amino-4-(benzylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (135 mg).

mp: 163-164.5°C (ethanol - diisopropyl ether)

IR (KBr): 3388, 3307, 3257, 3195, 1651, 1628, 1583, 1562 cm^{-1}

ESI/MS: 847[2M+Na]$^+$, 835[M+Na]$^+$, 813[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.11(6H, d, J=6.64 Hz), 4.64(2H, d, J=5.02 Hz), 5.03(2H, br.s), 5.21(1H, 7-plet, J=6.64 Hz), 6.45(2H, s), 7.16(1H, t, J=4.87 Hz), 7.13-7.42(10H, m)

Example 120

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and benzylamine (105 μl) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added and the mixture was stirred. An aqueous layer was removed by decantation. A residue was dissolved in chloroform, dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give 6-{2-amino-4-[benzyl(methyl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (126 mg).

mp: 167-168°C (ethanol - diisopropyl ether)

IR (KBr): 3496, 3273, 3118, 1657, 1622, 1589, 1554, 1531 cm^{-1}

ESI/MS: 449[M+Na]$^+$, 427[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.15(6H, d, J=6.60 Hz), 2.67(3H, s), 4.74(2H, s), 4.92(2H, br.s), 5.20(1H, 7-plet, J=6.60 Hz), 6.53(1H, d,

J=9.50 Hz), 6.76(1H, d, J=9.50 Hz), 7.13-7.35(10H, m)
Elemental Analysis for $C_{25}H_{26}N_6O$
Calcd.: C,70.40; H,6.14; N,19.70
Found : C,70.18; H,6.19; N,19.64

Example 121

6-{2-Amino-4-phenyl-6-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-pyridinylmethylamine according to a similar manner to that of Example 120.
mp: 196-198°C (ethanol)
IR (KBr): 3475, 3367, 3327, 3165, 1657, 1653, 1626, 1587, 1550, 1518 cm^{-1}
ESI/MS: 436$[M+Na]^+$, 414$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 1.40(6H, d, J=6.60 Hz), 4.80(2H, d, J=4.72 Hz), 5.06(2H, br.s), 5.33(1H, 7-plet, J=6.60 Hz), 6.51(2H, s), 7.15-7.40(7H, m), 7.62-7.70(2H, m), 8.49-8.53(1H, m)
Elemental Analysis for $C_{23}H_{23}N_7O \cdot 0.5H_2O$
Calcd.: C,65.39; H,5.73; N,23.21
Found : C,65.47; H,5.74; N,23.24

Example 122

6-{2-Amino-4-phenyl-6-[(3-pyridinylmethyl)amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 3-pyridinylmethylamine according to a similar manner to that of Example 120.
mp: 215-216.5°C (ethanol - diisopropyl ether)
IR (KBr): 3498, 3344, 3296, 3140, 1657, 1630, 1585, 1554 cm^{-1}
ESI/MS: 436$[M+Na]^+$, 414$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 1.19(6H, d, J=6.61 Hz), 4.68(2H, d, J=5.40 Hz), 5.02(2H, br.s), 5.26(1H, 7-plet, J=6.61 Hz), 6.47(2H, s), 7.25-7.43(7H, m), 7.66-7.73(1H, m), 8.55(1H, dd, J=1.54,

4.77 Hz), 8.64(1H, d, J=2.04 Hz)
Elemental Analysis for $C_{23}H_{23}N_7O$
Calcd.: C,66.81; H,5.61; N,23.71
Found : C,66.54; H,5.65; N,23.47

Example 123

6-{2-Amino-4-phenyl-6-[(4-pyridinylmethyl)amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 4-pyridinylmethylamine according to a similar manner to that of Example 120.
mp: 221.5-222.5°C (ethanol - diisopropyl ether)
IR (KBr): 3321, 3195, 1658, 1633, 1587, 1554 cm^{-1}
ESI/MS: 436$[M+Na]^+$, 414$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 1.26(6H, d, J=6.62 Hz), 4.71(2H, d, J=5.70 Hz), 4.98(2H, br.s), 5.30(1H, 7-plet, J=6.62 Hz), 6.49(2H, s), 7.26-7.43(8H, m), 8.56-8.60(2H, m)
Elemental Analysis for $C_{23}H_{23}N_7O$
Calcd.: C,66.81; H,5.61; N,23.71
Found : C,66.76; H,5.76; N,23.68

Example 124

6-{2-Amino-4-[(2-furylmethyl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-furylmethylamine according to a similar manner to that of Example 120.
mp: 213-214°C (ethanol)
IR (KBr): 3361, 3319, 3199, 1668, 1643, 1591, 1547 cm^{-1}
ESI/MS: 425$[M+Na]^+$, 403$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 1.10(6H, d, J=6.60 Hz), 4.54(2H, d, J=5.51 Hz), 5.05(1H, 7-plet, J=6.60 Hz), 6.31-6.41(2H, m), 6.45(2H, br.s), 6.67(1H, d, J=9.53 Hz), 6.87(1H, d, J=9.53 Hz), 7.00(1H, t, J=5.51 Hz), 7.22-7.31(5H, m), 7.55-7.57(1H, m)
Elemental Analysis for $C_{22}H_{22}N_6O_2$

Calcd.: C,65.66; H,5.51; N,20.88

Found : C,65.43; H,5.59; N,20.74

Example 125

6-[2-Amino-4-phenyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and pyrrolidine according to a similar manner to that of Example 115.

mp: >300°C (ethanol)

IR (KBr): 3500, 3276, 3143, 2966, 1666, 1622, 1589, 1552, 1531 cm^{-1}

ESI/MS: 775[2M+Na]$^+$, 399[M+Na]$^+$, 377[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.10(6H, d, J=6.60 Hz), 1.70-1.77(4H, m), 3.12-3.18(4H, m), 5.07(1H, 7-plet, J=6.60 Hz), 6.28(2H, br.s), 6.63(1H, d, J=9.48 Hz), 7.06-7.25(6H, m)

Elemental Analysis for $C_{21}H_{24}N_6O$

Calcd.: C,67.00; H,6.43; N,22.32

Found : C,66.75; H,6.52; N,22.19

Example 126

6-[2-Amino-4-phenyl-6-(1-piperidinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and piperidine according to a similar manner to that of Example 115.

mp: 221-223°C (ethanol - diisopropyl ether)

IR (KBr): 3498, 3286, 3157, 1658, 1621, 1585, 1550 cm^{-1}

ESI/MS: 413[M+Na]$^+$, 391[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.02(6H, d, J=6.60 Hz), 1.46-1.53(6H, m), 3.21-3.27(4H, m), 4.98(2H, br.s), 5.16(1H, 7-plet, J=6.60 Hz), 6.79(1H, d, J=9.50 Hz), 7.09(1H, d, J=9.50 Hz), 7.11-7.27(5H, m)

Elemental Analysis for $C_{22}H_{26}N_6O$

Calcd.: C,67.67; H,6.71; N,21.52

Found : C,67.54; H,6.82; N,21.43

Example 127

6-[2-Amino-4-(4-morpholinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and morpholine according to a similar manner to that of Example 115.

mp: 251-253°C (ethanol)

IR (KBr): 3498, 3276, 3149, 1660, 1621, 1589, 1554, 1539 cm^{-1}

ESI/MS: 807$[2M+Na]^+$, 415$[M+Na]^+$, 393$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.02(6H, d, J=6.60 Hz), 3.27(4H, t, J=4.69 Hz), 3.63(4H, t, J=4.69 Hz), 5.03(2H, br.s), 5.16(1H, 7-plet, J=6.60 Hz), 6.80(1H, d, J=9.46 Hz), 7.09(1H, d, J=9.46 Hz), 7.12-7.28(5H, m)

Elemental Analysis for $C_{21}H_{24}N_6O_2$

Calcd.: C,64.27; H,6.16; N,21.41

Found : C,64.03; H,6.27; N,21.21

Example 128

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and piperazine (1.748 g) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was colleted by filtration and purified by column chromatography on silica gel (methanol - ethyl acetate 10 : 90 v/v) to give 6-[2-amino-4-phenyl-6-(1-piperazinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (80 mg).

mp: 254-256°C (ethanol - diisopropyl ether)

IR (KBr): 3496, 3285, 3155, 1657, 1620, 1585, 1552, 1527 cm^{-1}

ESI/MS: 805$[2M+Na]^+$, 414$[M+Na]^+$, 392$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.92(6H, d, J=6.60 Hz), 2.57-2.63(4H, m), 3.07-3.12(4H, m), 4.97(1H, 7-plet, J=6.60 Hz), 6.54(2H, br.s), 6.80(1H, d, J=9.52 Hz), 7.06-7.14(2H, m), 7.22-7.28(3H, m),

7.30(1H, d, J=9.52 Hz)

Elemental Analysis for $C_{21}H_{25}N_7O \cdot 0.1H_2O$

Calcd.: C,64.14; H,6.46; N,24.93

Found : C,64.07; H,6.56; N,24.66

Example 129

6-[2-Amino-4-(4-methyl-1-piperazinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 1-methylpiperazine according to a similar manner to that of Example 114.

mp: 213-215°C (ethanol - diisopropyl ether)

IR (KBr): 3502, 3288, 3163, 1658, 1622, 1587, 1552, 1539 cm^{-1}

ESI/MS: 833$[2M+Na]^+$, 428$[M+Na]^+$, 406$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.92(6H, d, J=6.60 Hz), 2.13(3H, s), 2.21-2.26(4H, m), 3.14-3.18(4H, m), 4.98(1H, 7-plet, J=6.60 Hz), 6.58(2H, br.s), 6.81(1H, d, J=9.52 Hz), 7.06-7.14(2H, m), 7.22-7.32(4H, m)

Elemental Analysis for $C_{22}H_{27}N_7O$

Calcd.: C,65.16; H,6.71; N,24.18

Found : C,65.03; H,6.81; N,24.10

Example 130

Sodium hydride (60 % in oil suspension) (19.5 mg) was added to a solution of imidazole (35.9 mg) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixtutre and the mixture was heated at 100-105°C for 15 hours. Water (3 ml) was added to give a solid. The solid was collected by filtration and purified by column chromatography on silica gel (methanol - ethyl acetate 3 : 97 v/v) to give 6-[2-amino-4-(1H-imidazol-1-yl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (44 mg).

mp: 255-258°C (ethanol)

IR (KBr): 3440, 3136, 1637, 1589, 1574, 1529 cm^{-1}

ESI/MS: 396$[M+Na]^+$, 374$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.95(6H, d, J=6.61 Hz), 4.99(1H, 7-plet, J=6.61 Hz), 6.74(1H, d, J=9.50 Hz), 6.97-7.03(2H, m), 7.13(1H, s), 7.23-7.46(7H, m), 7.76(1H, s)

Example 131

6-[2-Amino-4-phenyl-6-(1H-1,2,4-triazol-1-yl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 1H-1,2,4-triazole according to a similar manner to that of Example 130.

mp: 266-268°C (ethanol)

IR (KBr): 3309, 3165, 1666, 1647, 1595, 1531 cm^{-1}

ESI/MS: 771$[2M+Na]^+$, 397$[M+Na]^+$, 375$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 0.88(6H, d, J=6.62 Hz), 4.97(1H, 7-plet, J=6.62 Hz), 6.69(1H, d, J=9.52 Hz), 7.07(1H, d, J=9.52 Hz), 7.24-7.38(5H, m), 7.51(2H, br.d), 8.10(1H, s), 9.13(1H, s)

Elemental Analysis for $C_{19}H_{18}N_8O \cdot 0.1H_2O$

Calcd.: C,60.66; H,4.88; N,29.79

Found : C,60.65; H,4.89; N,29.59

Example 132

6-[2-Amino-4-(1H-benzimidazol-1-yl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 1H-benzimidazole according to a similar manner to that of Example 130.

mp: 242-244°C (ethanol)

IR (KBr): 3464, 3298, 3167, 3103,1660, 1591, 1571 cm^{-1}

ESI/MS: 869$[2M+Na]^+$, 446$[M+Na]^+$, 424$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.92(6H, d, J=6.62 Hz), 5.08(1H, 7-plet, J=6.62 Hz), 5.53(2H, br.s), 6.55(1H, d, J=9.54 Hz), 6.60(1H,

d, J=9.54 Hz), 7.19-7.47(7H, m), 7.45-7.55(1H, m), 7.78-7.80(1H, m), 7.99(1H, s)

Elemental Analysis for $C_{24}H_{21}N_7O$

Calcd.: C,68.07; H,5.00; N,23.15

Found : C,67.77; H,5.01; N,23.07

Example 133

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (185 mg) and benzylamine (91.3 ml) in N,N-dimethylacetamide (0.37 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was dissolved in chloroform, dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (ethyl acetate) to give 6-(2-amino-4-anilino-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (73 mg).

mp: 240-242°C (ethanol)

IR (KBr): 3375, 3305, 3190, 1668, 1633, 1593, 1570, 1495 cm^{-1}

ESI/MS: 819[2M+Na]$^+$, 421[M+Na]$^+$, 399[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.51(6H, d, J=6.61 Hz), 5.10(1H, br.s), 5.43(1H, 7-plet, J=6.61 Hz), 6.51(2H, s), 7.10-7.59(10H, m), 8.94(1H, br.s)

Elemental Analysis for $C_{23}H_{22}N_6O \cdot 0.1H_2O$

Calcd.: C,69.02; H,5.59; N,21.00

Found : C,69.05; H,5.69; N,20.75

Example 134

6-{2-Amino-4-[(4,5-dimethyl-1,3-thiazol-2-yl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone, 4,5-dimethyl-1,3-thiazol-2-amine hydrochloride and N-ethyl-N,N-diisopropylamine according to a similar manner

to that of Example 133.

mp: 256-257.5°C (ethanol)

IR (KBr): 3415, 3321, 3155, 1651, 1626, 1576, 1541 cm^{-1}

ESI/MS: 456$[M+Na]^+$, 434$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 1.07(6H, d, J=6.60 Hz), 2.11(3H, s), 2.23(3H, s), 5.05(1H, 7-plet, J=6.60 Hz), 6.70-6.76(3H, m), 7.05-7.33(6H, m), 12.7(1H, br.s)

Elemental Analysis for $C_{22}H_{23}N_7OS$

Calcd.: C,60.95; H,5.35; N,22.62

Found : C,60.89; H,5.40; N,22.49

Example 135

6-[2-Amino-4-phenyl-6-(2-pyridinylamino)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-pyridinylamine according to a similar manner to that of Example 133.

mp: 163-164°C (acetone - hexane)

IR (KBr): 3491, 3300, 3180, 1668, 1630, 1591, 1545 cm^{-1}

ESI/MS: 821$[2M+Na]^+$, 422$[M+Na]^+$, 400$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.55(6H, d, J=6.60 Hz), 5.14(2H, br.s), 5.41(1H, 7-plet, J=6.60 Hz), 6.54(2H, s), 6.92-7.00(1H, m), 7.33-7.45(5H, m), 7.64-7.74(1H, m), 8.24-8.26(1H, m), 8.46(1H, d, J=8.48 Hz), 9.45(1H, br.s)

Elemental Analysis for $C_{22}H_{21}N_7O \cdot 0.2H_2O$

Calcd.: C,65.56; H,5.35; N,24.33

Found : C,65.66; H,5.30; N,24.43

Example 136

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (200 mg) and potassium fluoride (95 mg) in dimethylsulfoxide (1 ml) was heated at 100-105°C for 15 hours. Water (20 ml) was added to give a solid. The solid was colleted by filtration and purified

by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-(2-amino-4-fluoro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (35 mg).

mp: 231-232.5°C (ethanol)

IR (KBr): 3396, 3325, 3197, 1647, 1631, 1612, 1581, 1504 cm^{-1}

ESI/MS: 673[2M+Na]$^+$, 348[M+Na]$^+$, 326[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.03(6H, d, J=6.63 Hz), 5.18(1H, 7-plet, J=6.63 Hz), 5.46(2H, br.s), 6.84(1H, d, J=9.52 Hz), 7.09(1H, dd, J=1.90,9.52 Hz), 7.28-7.37(5H, m)

Elemental Analysis for $C_{17}H_{16}FN_5O \cdot 0.2H_2O$

Calcd.: C,62.07; H,5.02; N,21.29

Found : C,62.24; H,4.92; N,21.10

Example 137

A solution of 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (193 mg) and guanidine carbonate (92 mg) in N,N-dimethylacetamide (0.38 ml) was heated at 100-105°C for 15 hours. Water (3 ml) was added to give a solid. The solid was collected by filtration and dried over phosphorous pentoxide to give N-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]guanidine as a solid (136 mg).

mp: 272-274.5°C (N,N-dimethylacetamide - water)

IR (KBr): 3348, 1622, 1564, 1510 cm^{-1}

ESI/MS: 751[2M+Na]$^+$, 365[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.69(6H, d, J=6.62 Hz), 4.85(1H, 7-plet, J=6.62Hz), 6.35(2H, br.s), 6.72(1H, d, J=9.50Hz), 7.00-7.29(9H, m), 7.55(1H, d, J=9.50 Hz)

Elemental Analysis for $C_{18}H_{20}N_8O \cdot 0.5H_2O$

Calcd.: C,57.90; H,5.67; N,30.01

Found : C,58.16; H,5.49; N,29.82

Example 138

6-[2-Amino-4-phenyl-6-(phenylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and benzenethiol according to a similar manner to that of Example 95.

mp: 214-215°C (ethanol)

IR (KBr): 3444, 3313, 3199, 1670, 1620, 1593, 1539, 1520 cm^{-1}

ESI/MS: 853$[2M+Na]^+$, 438$[M+Na]^+$, 416$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.32(6H, d, J=6.63 Hz), 5.02(2H, br.s), 5.33(1H, 7-plet, J=6.63 Hz), 6.72(1H, d, J=9.50 Hz), 6.86(1H, d, J=9.50 Hz), 7.29-7.56(10H, m)

Elemental Analysis for $C_{23}H_{21}N_5OS$

Calcd.: C,66.48; H,5.09; N,16.85

Found : C,66.31; H,5.12; N,16.83

Example 139

To a solution of 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (5.00 g) in methanol (100 ml) was added a 28 % solution of sodium methoxide in methanol (13.6 ml) and the mixture was refluxed for 36 hours. After cooling at ambient temperature, a precipitate was collected by filtration and dried under reduced pressure to give 6-(2-amino-4-methoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (3.76 g).

mp: 230-233°C (ethanol)

IR (KBr): 3519, 3394, 1660, 1606, 1581, 1543 cm^{-1}

ESI/MS: 697$[2M+Na]^+$, 360$[M+Na]^+$, 338$[M+H]^+$

ESI/MS-Neg: 336$[M-H]^-$

^1H NMR ($CDCl_3$, δ): 0.92(6H, d, J=6.62 Hz), 3.95(3H, s), 5.11(1H, 7-plet, J=6.62 Hz), 5.22(2H, br.s), 6.84(1H, d, J=9.52 Hz), 7.21-7.30(6H, m)

Elemental Analysis for $C_{18}H_{19}N_5O_2$

Calcd.: C,64.08; H,5.68; N,20.76

Found : C,64.24; H,5.64; N,20.75

Example 140

A mixture of 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (535 mg) and urea hydrogen peroxide addition compound (143 mg) in acetic acid (0.8 ml) was heated at 70-75°C for 1 hour. Urea hydrogen peroxide addition compound (143 mg) was added and the mixture was stirred at the same temperature. After 1 hour, urea hydrogen peroxide addition compound (143 mg) was added and the mixture was heated at 70-75°C for 3 hours. Water (12 ml) was added to the mixture. A precipitate was collected by filtration, washed with chloroform and dried under reduced pressure to give 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (298 mg).

mp: 291-295°C (acetic acid - water)

IR (KBr): 3363, 3126, 1645, 1576, 1500 cm^{-1}

ESI/MS: 669[2M+Na]$^+$, 346[M+Na]$^+$, 324[M+H]$^+$

^{1}H NMR (DMSO-d_6, δ): 0.72(6H, d, J=6.62 Hz), 4.87(1H, 7-plet, J=6.62 Hz), 6.82(1H, d, J=9.55 Hz), 6.91(2H, br.s), 7.17-7.30(4H, m), 7.47-7.50(2H, m), 11.33(1H, br.s)

Elemental Analysis for $C_{17}H_{17}N_5O_2 \cdot 0.8H_2O$

Calcd.: C,60.45; H,5.55; N,20.73

Found : C,60.35; H,5.46; N,20.38

Example 141

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (300 mg) and potassium thioacetate (111 mg) in N,N-dimethylacetamide (0.6 ml) was heated at 100-105°C for one hour. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel. With an elution of a mixture of n-hexane and ethyl acetate (40 : 60 v/v) was given S-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]ethanethioate as a

solid (8 mg). Next, with an elution of a mixture of n-hexane and ethyl acetate (20 : 80 v/v) was given 6-(2-amino-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (73 mg).

S-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]ethanethioate
mp: 240°C (ethanol - diisopropyl ether)
ESI/MS: 404[M+Na]$^+$, 382[M+H]$^+$
^{1}H NMR ($CDCl_3$, δ): 0.86(6H, d, J=6.62 Hz), 2.28(3H, s), 5.08(1H, 7-plet, J=6.62 Hz), 6.93(1H, d, J=9.46 Hz), 7.17-7.41(6H, m), 7.60(1H, d, J=9.46 Hz), 9.08(1H, br.s)

6-(2-amino-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone
mp: 295-299°C (ethanol suspension)
IR (KBr): 1647, 1558 cm^{-1}
ESI/MS: 701[2M+Na]$^+$, 362[M+Na]$^+$, 340[M+H]$^+$
^{1}H NMR (DMSO-d_6, δ): 0.74(6H, d, J=6.60 Hz), 4.88(1H, 7-plet, J=6.60 Hz), 6.80(1H, d, J=9.50 Hz), 7.04-7.30(7H, m), 7.62(1H, d, J=9.50 Hz), 12.60(1H, br.s)

Example 142

6-[2-Amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-methyl-3(2H)-pyridazinone and guanidine carbonate according to a similar manner to that of Example 78.
mp: 233-235°C (chloroform - diisopropyl ether)
IR (KBr): 3406, 3315, 3217, 1647, 1624, 1581, 1537 cm^{-1}
ESI/MS: 673[2M+Na]$^+$, 348[M+Na]$^+$, 326[M+H]$^+$
^{1}H NMR ($CDCl_3$, δ): 2.49(3H, s), 3.80(3H, s), 5.23(2H, br.s), 6.71(1H, d, J=9.52 Hz), 6.77(1H, d, J=9.52 Hz), 7.26-7.41(5H,

m)

^{1}H NMR (DMSO-d_6, δ): 2.45(3H, s), 3.60(3H, s), 6.79(1H, d, J=9.52 Hz), 7.03(2H, br.s), 7.09(1H, d, J=9.52 Hz), 7.34(5H, s)

Example 143

6-[2-Amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and 3-chloroperbenzoic acid according to a similar manner to that of Example 79.

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone

mp: >250°C (ethanol suspension)

IR (KBr): 3498, 3294, 1668, 1618, 1593, 1554, 1516 cm^{-1}

ESI/MS-Neg: 340$[M-H]^-$

^{1}H NMR ($CDCl_3$, δ): 3.04(3H, s), 3.84(3H, s), 6.06(2H, br.s), 6.56(1H, d, J=9.52 Hz), 6.65(1H, d, J=9.52 Hz), 7.34-7.52(5H, m)

^{1}H NMR (DMSO-d_6, δ): 2.90(3H, s), 3.67(3H, s), 6.72(1H, d, J=9.56 Hz), 6.92(1H, d, J=9.56 Hz), 7.37-7.46(5H, m), 7.62(2H, br.s)

6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone

mp: 240-243°C (ethanol suspension)

IR (KBr): 3340, 3305, 3190, 1643, 1566 cm^{-1}

ESI/MS: 737$[2M+Na]^+$, 380$[M+Na]^+$, 358$[M+H]^+$

^{1}H NMR ($CDCl_3$, δ): 3.30(3H, s), 3.77(3H, s), 5.60(2H, br.s), 6.75(1H, d, J=9.54 Hz), 6.89(1H, d, J=9.54 Hz), 7.33-7.44(5H, m)

Example 144

6-(2-Amino-4-methoxy-6-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and sodium methoxide according to a similar manner to that of Example 80.

mp: 218-220°C (ethanol - diisopropyl ether)

IR (KBr): 3421, 1649, 1577 cm^{-1}

ESI/MS: 332$[M+Na]^+$, 310$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 3.61(3H, s), 3.93(3H, s), 5.20(2H, br.s), 6.81(1H, d, J=9.52 Hz), 7.07(1H, d, J=9.52 Hz), 7.26-7.35(5H, m)

Example 145

6-[2-Amino-4-(benzylamino)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and benzylamine according to a similar manner to that of Example 120.

mp: >250°C (ethanol suspension)

IR (KBr): 3489, 3346, 3290, 1658, 1633, 1585, 1560 cm^{-1}

ESI/MS: 407$[M+Na]^+$, 385$[M+H]^+$

^1H NMR (DMSO-d_6, δ): 3.63(3H, s), 4.58(2H, d, J=6.01 Hz), 6.34(2H, br.s), 6.66(1H, d, J=9.52 Hz), 6.79(1H, d, J=9.52 Hz), 7.18-7.34(11H, m)

Example 146

6-{2-amino-4-phenyl-6-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and 2-pyridinylmethylamine according to a similar manner to that of Example 120.

mp: 248-250°C (ethanol suspension)

IR (KBr): 3473, 3278, 1664, 1631, 1589, 1576, 1554 cm^{-1}

ESI/MS: 408$[M+Na]^+$, 407$[M+H]^+$

^{1}H NMR (DMSO-d_6, δ): 3.71(3H, s), 4.67(2H, d, J=5.31 Hz), 6.41(2H, br.s), 6.64(1H, d, J=9.58 Hz), 6.75(1H, d, J=9.58 Hz), 7.24-7.85(7H, m), 7.73-7.85(2H, m), 8.52-8.55(1H, m)

Example 147

6-(2-Amino-4-anilino-6-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and aniline according to a similar manner to that of Example 133.

mp: 252-254°C (ethanol)

IR (KBr): 3384, 3307, 3149, 1662, 1649, 1580, 1549 cm^{-1}

ESI/MS: 393$[M+Na]^+$, 371$[M+H]^+$

^{1}H NMR ($CDCl_3$, δ): 3.92(3H, s), 5.08(2H, br.s), 6.54(2H, s), 7.08-7.63(10H, m), 9.23(1H, br.s)

Example 148

A mixture of 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[1-(4-fluorobenzoyl)-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone and guanidine carbonate according to a similar manner to that of Example 78.

6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 232-234°C (ethanol)

IR (KBr): 3516, 3313, 1658, 1587, 1547 cm^{-1}

ESI/MS: 394$[M+Na]^+$, 372$[M+H]^+$

^{1}H NMR ($CDCl_3$, δ): 1.27(6H, d, J=6.64 Hz), 2.49(3H, s), 5.16(2H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.74(1H, d, J=9.50 Hz), 6.83(1H, d, J=9.50 Hz), 6.94-7.03(2H, m), 7.26-7.37(2H, m)

Elemental Analysis for $C_{18}H_{18}FN_5O_2S$
Calcd.: C,58.21; H,4.88; N,18.86
Found : C,58.45; H,4.95; N,18.65

6-{2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone
ESI/MS: 821[2M+Na]$^+$, 422[M+Na]$^+$, 400[M+H]$^+$
^{1}H NMR (DMSO-d_6, δ): 1.30(6H, d, J=6.60 Hz), 2.46(3H, s), 2.48(3H, s)

Example 149

A mixture of 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from a mixture of 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and a solution of 28 % sodium methoxide in methanol according to a similar manner to that of Example 139.

6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 207-209°C (acetone)
IR (KBr): 3427, 3323, 3217, 1645, 1624, 1581 cm^{-1}
ESI/MS: 733[2M+Na]$^+$, 378[M+Na]$^+$, 356[M+H]$^+$
^{1}H NMR ($CDCl_3$, δ): 0.96(6H, d, J=6.60 Hz), 3.95(3H, s), 5.07-5.21(3H, m), 6.85(1H, d, J=9.52 Hz), 6.92-7.03(2H, m), 7.21-7.31(3H, m)

6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

ESI/MS: 789[2M+Na]$^+$, 406[M+Na]$^+$, 384[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 2.44(3H, s), 3.94(3H, s)

Example 150

6-[2-Amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone were prepared from a mixture of 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and 3-chloroperbenzoic acid according to a similar manner to that of Example 79.

6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 207-209°C (acetone)

IR (KBr): 3427, 3323, 3217, 1645, 1624, 1581 cm^{-1}

ESI/MS: 733[2M+Na]$^+$, 378[M+Na]$^+$, 356[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 0.96(6H, d, J=6.60 Hz), 3.95(3H, s), 5.07-5.21(3H, m), 6.85(1H, d, J=9.52 Hz), 6.92-7.03(2H, m), 7.21-7.31(3H, m)

6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

mp: 148-151°C (acetone)

IR (KBr): 1660, 1633, 1587, 1566, 1547 cm^{-1}

ESI/MS: 853[2M+Na]$^+$, 438[M+Na]$^+$, 416[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d, J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

^{1}H NMR (DMSO-d_6, δ): 0.69(6H, d, J=6.60 Hz), 3.15(3H, s), 3.90(3H, s), 4.90(1H, 7-plet, J=6.60 Hz), 6.91(1H, d, J=9.54 Hz), 7.12(2H, br.s), 7.45(2H, d, J=8.32 Hz), 7.57(1H, d, J=9.54 Hz), 7.87(2H, d, J=8.32 Hz)

Example 151

Under ice-cooling, 3-perbenzoic acid (70 % purity) (1.33 g) was added to a mixture of 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (1.47 g, molar ratio 6:4) in dichloromethane (15 ml). After stirring at the same temperature for 2 hours, the mixture was washed with saturated aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 10 : 90, ethyl acetate and methanol - ethyl acetate=4:96, 8:92, 10:90 v/v, in turn). Successively, 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (101 mg), 6-[2-amino-4-[4-(methylsulfonyl)-phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (41 mg), 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (510 mg) and 6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (54 mg) were isolated as a solid, respectively.

6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 232-234°C (ethanol)
IR (KBr): 3516, 3313, 1658, 1587, 1547 cm^{-1}

ESI/MS: 394[M+Na]$^+$, 372[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.27(6H, d, J=6.64 Hz), 2.49(3H, s), 5.16(2H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.74(1H, d, J=9.50 Hz), 6.83(1H, d, J=9.50 Hz), 6.94-7.03(2H, m), 7.26-7.37(2H, m)

6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 241-243°C (ethanol suspension)

IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm^{-1}

ESI/MS: 885[2M+Na]$^+$, 454[M+Na]$^+$, 432[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.16(6H, d, J=6.60 Hz), 2.52(3H, s), 3.01(3H, s), 5.17-5.35(3H, m), 6.80(1H, d, J=9.52 Hz), 6.99(1H, d, J=9.52 Hz), 7.52(2H, d, J=8.34 Hz), 7.89(2H, d, J=8.34 Hz)

6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 238-240°C (chloroform - acetone)

IR (KBr): 3506, 3290, 3180, 1667, 1625, 1597, 1552 cm^{-1}

ESI/MS: 797[2M+Na]$^+$, 410[M+Na]$^+$, 388[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.37(3H, d, J=6.64 Hz), 1.40(3H, d, J=6.64 Hz), 2.98(3H, s), 5.40(1H, 7-plet, J=6.64 Hz), 5.75(2H, br.s), 6.61(1H, d, J=9.54 Hz), 6.70(1H, d, J=9.54 Hz), 7.02-7.13(2H, m), 7.35-7.44(2H, m)

^{1}H NMR (DMSO-d_6, δ): 1.19(6H, d, J=6.60 Hz), 2.85(3H, s), 5.13(2H, 7-plet), 6.77(1H, d, J=9.53 Hz), 7.09(1H, d, J=9.53 Hz), 7.18-7.41(4H, m), 7.63(2H, br.s)

Elemental Analysis for $C_{18}H_{18}FN_5O_2$

Calcd.: C,58.21; H,4.88; N,18.86

Found : C,58.45; H,4.95; N,18.65

6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

ESI/MS: 454[M+Na]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.33(3H, d, J=6.61 Hz), 1.38(3H, d, J=6.61 Hz), 2.73(3H, s), 2.98(3H, s), 5.77(2H, br.s), 5.38(1H, 7-plet, J=6.61 Hz), 6.65(1H, d, J=9.56 Hz), 6.70(1H, d, J=9.56 Hz), 7.53-7.70(4H, m)

^{1}H NMR (DMSO-d_6, δ): 1.10(6H, d, J=6.63 Hz), 2.73(3H, s), 2.86(3H, s), 5.10(1H, 7-plet, J=6.63 Hz), 6.78(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.48(2H, d, J=8.34 Hz), 7.63-7.71(4H, m)

Example 152

Successively,
6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (410 mg),
6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (257 mg),
6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (128 mg),
6-[2-amino-4-[4-(methylsulfinyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (405 mg) and
6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (248 mg) were isolated as a solid, respectively, from a mixture of
6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and
3-chloroperbenzoic acid (70 % purity) according to a similar manner to that of Example 151.

6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 232-234°C (ethanol)
IR (KBr): 3516, 3313, 1658, 1587, 1547 cm^{-1}
ESI/MS: 394[M+Na]$^+$, 372[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 1.27(6H, d, J=6.64 Hz), 2.49(3H, s), 5.16(2H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.74(1H, d, J=9.50 Hz), 6.83(1H, d, J=9.50 Hz), 6.94-7.03(2H, m), 7.26-7.37(2H, m)

6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 241-243°C (ethanol suspension)
IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm^{-1}
ESI/MS: 885$[2M+Na]^+$, 454$[M+Na]^+$, 432$[M+H]^+$
^{1}H NMR ($CDCl_3$, δ): 1.16(6H, d, J=6.60 Hz), 2.52(3H, s), 3.01(3H, s), 5.17-5.35(3H, m), 6.80(1H, d, J=9.52 Hz), 6.99(1H, d, J=9.52 Hz), 7.52(2H, d, J=8.34 Hz), 7.89(2H, d, J=8.34 Hz)

6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 238-240°C (chloroform - acetone)
IR (KBr): 3506, 3290, 3180, 1667, 1625, 1597, 1552 cm^{-1}
ESI/MS: 797$[2M+Na]^+$, 410$[M+Na]^+$, 388$[M+H]^+$
^{1}H NMR ($CDCl_3$, δ): 1.37(3H, d, J=6.64 Hz), 1.40(3H, d, J=6.64 Hz), 2.98(3H, s), 5.40(1H, 7-plet, J=6.64 Hz), 5.75(2H, br.s), 6.61(1H, d, J=9.54 Hz), 6.70(1H, d, J=9.54 Hz), 7.02-7.13(2H, m), 7.35-7.44(2H, m)
^{1}H NMR (DMSO-d_6, δ): 1.19(6H, d, J=6.60 Hz), 2.85(3H, s), 5.13(2H, 7-plet), 6.77(1H, d, J=9.53 Hz), 7.09(1H, d, J=9.53 Hz), 7.18-7.41(4H, m), 7.63(2H, br.s)
Elemental Analysis for $C_{18}H_{18}FN_5O_2S$
Calcd.: C,58.21; H,4.88; N,18.86
Found : C,58.45; H,4.95; N,18.65

6-[2-amino-4-[4-(methylsulfinyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 221-223°C (chloroform - acetone)

IR (KBr): 3390, 3302, 3203, 1658, 1583, 1539 cm^{-1}

ESI/MS: 438$[M+Na]^+$, 416$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.20(6H, d, J=6.62 Hz), 2.51(3H, s), 2.68(3H, s), 5.23-5.38(4H, m), 6.76(1H, d, J=9.52 Hz), 6.93(1H, d, J=9.52 Hz), 7.46-7.61(4H, m)

6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

mp: 241-243°C (ethanol suspension)

IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm^{-1}

ESI/MS: 885$[2M+Na]^+$, 454$[M+Na]^+$, 432$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.16(6H, d, J=6.60 Hz), 2.52(3H, s), 3.01(3H, s), 5.17-5.35(3H, m), 6.80(1H, d, J=9.52 Hz), 6.99(1H, d, J=9.52 Hz), 7.52(2H, d, J=8.34 Hz), 7.89(2H, d, J=8.34 Hz)

Example 153

6-{2-Amino-4-methoxy-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-[4-(methylsulfinyl)-phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and sodium methoxide according to a similar manner to that of Example 139.

mp: 127-130°C (chloroform - hexane)

IR (KBr): 3319, 3190, 1660, 1587, 1545 cm^{-1}

ESI/MS: 821$[2M+Na]^+$, 422$[M+Na]^+$

^1H NMR ($CDCl_3$, δ): 0.87(6H, d, J=6.62 Hz), 2.66(3H, s), 3.95(3H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.22(2H, br.s), 6.87(1H, d, J=9.52 Hz), 7.32(1H, d, J=9.52 Hz), 7.40-7.46(2H, m), 7.54-7.60(2H, m)

Example 154

6-{2-Amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared

from
6-[2-amino-4-[4-(methylsulfonyl)-phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and sodium methoxide according to a similar manner to that of Example 139.

mp: 148-151°C (acetone)

IR (KBr): 1660, 1633, 1587, 1566, 1547 cm^{-1}

ESI/MS: 853$[2M+Na]^+$, 438$[M+Na]^+$, 416$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d, J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

^1H NMR (DMSO-d_6, δ): 0.69(6H, d, J=6.60 Hz), 3.15(3H, s), 3.90(3H, s), 4.90(1H, 7-plet, J=6.60 Hz), 6.91(1H, d, J=9.54 Hz), 7.12(2H, br.s), 7.45(2H, d, J=8.32 Hz), 7.57(1H, d, J=9.54 Hz), 7.87(2H, d, J=8.32 Hz)

Example 155

6-{2-Amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from
6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and sodium methoxide according to a similar manner to that of Example 80.

mp: 148-151°C (acetone)

IR (KBr): 1660, 1633, 1587, 1566, 1547 cm^{-1}

ESI/MS: 853$[2M+Na]^+$, 438$[M+Na]^+$, 416$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d, J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

^1H NMR (DMSO-d_6, δ): 0.69(6H, d, J=6.60 Hz), 3.15(3H, s), 3.90(3H, s), 4.90(1H, 7-plet, J=6.60 Hz), 6.91(1H, d, J=9.54 Hz), 7.12(2H, br.s), 7.45(2H, d, J=8.32 Hz), 7.57(1H, d, J=9.54 Hz), 7.87(2H,

d, J=8.32 Hz)

Example 156

6-[2-Amino-4-(benzylamino)-6-(4-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and benzylamine according to a similar manner to that of Example 120.

mp: 191-192°C (ethanol)

IR (KBr): 3494, 3352, 3302, 1660, 1631, 1585, 1566, 1552 cm^{-1}

ESI/MS: 453$[M+Na]^+$, 431$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.12(6H, d, J=6.62 Hz), 4.63(2H, d, J=5.02 Hz), 5.00(2H, br.s), 5.22(1H, 7-plet, J=6.62 Hz), 6.46(1H, d, J=9.56 Hz), 6.99(1H, d, J=9.56 Hz), 6.97-7.44(10H, m)

Example 157

6-{2-Amino-4-(4-fluorophenyl)-6-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-pyridinylmethylamine according to a similar manner to that of Example 120.

mp: 210-212°C (ethanol)

IR (KBr): 3375, 3303, 1660, 1589, 1552 cm^{-1}

ESI/MS: 454$[M+Na]^+$, 432$[M+H]^+$

^1H NMR ($CDCl_3$, δ): 1.40(6H, d, J=6.63 Hz), 4.79(2H, d, J=4.64 Hz), 4.98(2H, br.s), 5.34(1H, 7-plet, J=6.63 Hz), 6.51(1H, d, J=9.56 Hz), 6.57(1H, d, J=9.56 Hz), 6.96-7.06(2H, m), 7.21-7.43(4H, m), 7.63-7.69(2H, m), 8.50-8.53(1H, m)

Example 158

6-[2-Amino-4-anilino-6-(4-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-

5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and aniline (according to a similar manner to that of Example 133.
mp: >250°C (ethanol suspension)
IR (KBr): 3450, 3305, 3192, 1657, 1628, 1601, 1581, 1552 cm^{-1}
ESI/MS: 417$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 1.51(6H, d, J=6.63 Hz), 5.07(2H, br.s), 5.43(1H, 7-plet, J=6.63 Hz), 6.52(1H, d, J=9.62 Hz), 6.59(1H, d, J=9.62 Hz), 7.00-7.59(9H, m), 8.91(1H, s)

Example 159

A mixture of 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (324 mg) and sodium hydride (60 % in oil suspension) (42 mg) in N,N-dimethylacetamide (1 ml) was heated at 50-55°C for 30 minutes. tert-Butyl bromoacetate (163 ml) was added to the mixture and the mixture was stirred at the same temperature for 3 hours. Water (5 ml) was added, stirred at ambient temperature and removed by decantation to give syrup. The syrup was purified by column chromatography on silica gel. With an elution of a mixture of n-hexane and ethyl acetate (50 : 50 v/v) was given tert-butyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate as a solid (50 mg). With an elution of ethyl acetate was given tert-butyl [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-oxo-4-phenyl-1(6H)-pyrimidinyl]acetate as a solid (265 mg).

tert-butyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]-oxy}acetate
mp: 160-162°C (acetone)
IR (KBr): 3431, 3309, 3195, 1745, 1658, 1635, 1591, 1545 cm^{-1}
ESI/MS: 460$[M+Na]^+$, 438$[M+H]^+$
^1H NMR ($CDCl_3$, δ): 0.88(6H, d, J=6.62 Hz), 1.50(9H, s), 4.80(2H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.12(2H, br.s), 6.87(1H, d,

J=9.52 Hz), 7.23-7.29(5H, m), 7.45(1H, d, J=9.52 Hz)
Elemental Analysis for $C_{23}H_{27}N_5O$
Calcd.: C,63.14; H,6.22; N,16.01
Found : C,63.09; H,6.29; N,15.90

tert-butyl [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-oxo-4-phenyl-1(6H)-pyrimidinyl]acetate
mp: 138-141°C (acetone suspension)
IR (KBr): 3342, 3219, 1755, 1705, 1645, 1583, 1535 cm^{-1}
ESI/MS: 897[2M+Na]$^+$, 460[M+Na]$^+$, 438[M+H]$^+$
^{1}H NMR ($CDCl_3$, δ): 0.84(6H, d, J=6.60 Hz), 1.52(9H, s), 4.75(2H, s), 5.06(1H, 7-plet, J=6.60 Hz), 5.38(2H, br.s), 6.86(1H, d, J=9.52 Hz), 7.25-7.28(5H, m), 7.46(1H, d, J=9.52 Hz)

Example 160

6-[2-amino-4-(2-oxopropoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone and 1-chloroacetone according to a similar manner to that of Example 159.
ESI/MS: 781[2M+Na]$^+$, 402[M+Na]$^+$, 380[M+H]$^+$
^{1}H NMR ($CDCl_3$, δ): 0.92(6H, d, J=6.62 Hz), 2.21(3H, s), 4.94(2H, s), 5.11(1H, 7-plet, J=6.62 Hz), 5.19(2H, br.s), 6.86(1H, d, J=9.50 Hz), 7.26-7.29(5H, m), 7.40(1H, d, J=9.50 Hz)

Example 161

6-[2-Amino-4-(2-oxo-2-phenylethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone and 2-bromo-1-phenylethanone according to a similar manner to that of Example 159.
mp: 182-183°C (diisopropyl ether - hexane)
IR (KBr): 3375, 3168, 1709, 1660, 1587 cm^{-1}
ESI/MS: 905[2M+Na]$^+$, 464[M+Na]$^+$, 442[M+H]$^+$

^{1}H NMR ($CDCl_3$, δ): 0.90(6H, d, J=6.60 Hz), 5.05(2H, br.s), 5.10(1H, 7-plet, J=6.60 Hz), 5.69(2H, s), 6.87(1H, d, J=9.52 Hz), 7.26-7.28(5H, m), 7.48-7.70(4H, m), 7.95-8.01(2H, m)

Example 162

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (62.4 mg) was dissolved in pyridine (5 ml). To the solution was added isoamyloyl chloride (32 mg) at 25°C. The solution was stirred for 2 hour at 25°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and washes with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was dissolved in chloroform and submitted to silica gel (31.4 ml) column. The column was eluted with chloroform-methanol (9:1). Evaporation of solvent of the fractions containing product gave crystals. Recrystallization from 80%-aqeous ethanol gave pure crystals of N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-3-methylbutanamide (33.4 mg)

^{1}H NMR (DMSO-d_6, δ): 0.94(6H, d, J=6.6 Hz), 1.04(6H, d, J=6.6 Hz), 2.03-2.16(1H, m), 2.42(2H, d, J=7 Hz), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H,s), 8.85(1H, s), 10.8(1H, s)

ESI/MS: 392$[M+H]^+$, 414$[M+Na]^+$

IR (KBr): 3255, 2958, 1722, 1660, 1589, 1484, 1446 cm^{-1}

mp: 161°C (aq-EtOH)

Example 163

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2-methylpropanamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 1.10(6H, d, J=6.8 Hz), 2.84-2.98(1H, m), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.85(1H, s), 10.8(1H, s)

ESI/MS: 378[M+H]$^+$, 400[M+Na]$^+$

IR (KBr): 3255, 2958, 1730, 1660, 1587, 1484, 1446 cm^{-1}

mp: 145-147°C (aq-EtOH)

Example 164

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]butanamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 0.92(3H, d, J=7.4 Hz), 1.04(6H, d, J=6.6 Hz), 1.56-1.67(2H, m), 2.53(2H, t, J=7.4 Hz), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.85(1H, s), 10.8(1H, s)

ESI/MS: 378[M+H]$^+$, 400[M+Na]$^+$

IR (KBr): 3255, 2958, 1725, 1660, 1583, 1484, 1446 cm^{-1}

mp: 148-150°C (aq-EtOH)

Example 165

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]cyclohexanecarboxamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 1.18-1.87(10H, m), 2.69-2.74(1H, m), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.31(1H, d, J=9.6 Hz), 7.43(5H, s), 8.84(1H, s), 10.7(1H, s)

ESI/MS: 418[M+H]$^+$, 440[M+Na]$^+$

IR (KBr): 3255, 2956, 1732, 1660, 1585, 1484, 1446 cm^{-1}

mp: 195-198°C (aq-EtOH)

Example 166

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2-methoxyacetamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 3.36(3H, s), 4.31(2H, s), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 380[M+H]$^+$, 402[M+Na]$^+$

IR (KBr): 3250, 2955, 1730, 1660, 1580, 1484, 1446 cm^{-1}

mp: 94-97°C (aq-EtOH)

Example 167

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]cyclopropanecarboxamide was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO-d_6, δ): 0.85(4H, d, J=5.6 Hz), 1.04(6H, d, J=6.6 Hz), 2.19(1H, t, J=5.6 Hz), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 398$[M+Na]^+$

IR (KBr): 3255, 2958, 1722, 1663, 1590, 1484, 1446 cm^{-1}

mp: 143-147°C (aq-EtOH)

Example 168

Methyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylcarbamate was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 3.70(2H, s), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.83(1H, s), 10.73(1H, s)

ESI/MS: 366$[M+H]^+$, 388$[M+Na]^+$

IR (KBr): 3255, 2958, 1722, 1660, 1589, 1484, 1446 cm^{-1}

mp: 197-200°C (aq-EtOH)

Example 169

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 5.05(1H, m), 6.93(1H, d, J=9.6 Hz), 7.40(1H, d, J=9.6 Hz), 7.44(5H, s), 7.44-7.66(3H, m), 8.00 (2H, m), 8.89(1H, s), 11.1(1H, s)

ESI/MS-Neg: 410$[M-H]^-$

IR (KBr): 3305, 2976, 1690,1660, 1585, 1481, 1442 cm^{-1}

mp: 116-120°C (aq-EtOH)

Example 170

4-Fuoro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 5.05(1H, m), 6.93(1H, d, J=9.6 Hz), 7.32-7.44(4H, m), 7.40(1H, d, J=9.6 Hz), 7.44(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 430$[M+H]^+$, 452$[M+Na]^+$

IR (KBr): 3305, 1660, 1585, 1481 cm^{-1}

mp: 106-110°C (aq-EtOH)

Example 171

4-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 5.06(1H, m), 6.92(1H, d, J=9.6 Hz), 7.39(1H, d, J=9.6 Hz), 7.44(5H, s), 7.60(2H, d, J=8.4 Hz), 8.01(2H, d, J=8.4 Hz), 8.95(1H, s), 11.4(1H, s)

ESI/MS: 446$[M+H]^+$, 468$[M+Na]^+$

IR (KBr): 3300, 1665, 1575, 1470 cm^{-1}

mp: 100°C (aq-EtOH)

Example 172

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methoxybenzamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 3.85(3H, s), 5.06(1H, m), 6.91(1H, d, J=9.6 Hz), 7.05(2H, d, J=8.8 Hz), 7.39(1H, d, J=9.6 Hz), 8.02(2H, d, J=8.8 Hz), 7.49(5H, s), 8.93(1H, s), 11.1(1H, s)

ESI/MS: 442$[M+H]^+$, 464.1$[M+Na]^+$

IR (KBr): 3250, 1670, 1580, 1470 cm^{-1}

mp: 171-174°C (aq-EtOH)

Example 173

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methylbenzamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 2.40(3H, s), 5.06(1H, m), 6.92(1H, d, J=9.6 Hz), 7.33(2H, d, J=8.0 Hz), 7.39(1H, d, J=9.6 Hz), 7.49(5H, s), 7.92(2H, d, J=8.0 Hz), 8.93(1H, s), 11.2(1H, s)

ESI/MS: 426$[M+H]^+$, 448$[M+Na]^+$

IR (KBr): 3350, 1675, 1560, 1475 cm^{-1}

mp: 116°C (aq-EtOH)

Example 174

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-(trifluoromethyl)benzamide was prepared according to a similar manner to that of Example 162.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 5.06(1H, m), 6.93(1H, d, J=9.6 Hz), 7.40(1H, d, J=9.6 Hz), 7.42(5H, s), 7.90(2H, d, J=8.4 Hz), 8.15(2H, d, J=8.4 Hz), 8.95(1H, s), 11.5(1H, s)

ESI/MS: 480$[M+H]^+$, 502$[M+Na]^+$

IR (KBr): 3320, 1685, 1555, 1484 cm^{-1}

mp: 160-163°C (aq-EtOH)

Example 175

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (122.8 mg) was dissolved in pyridine (10 ml). To the solution was added 3-picolyl chloride hydrochloride (142 mg) at room temperature. The solution was stirred for 2 hours, and stood overnight.

Concentration of the above reaction mixture gave crystal residue. To the residue was added H_2O (20 ml). Crystals were precipitated and collected by filtration. Recrstallization from 5%-aqeous ethanol gave pure crystals of

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]nicotinamide (157 mg).

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 5.05(1H, m), 6.93(1H, d, J=9.6 Hz), 7.39(1H, d, J=9.6 Hz), 7.44(5H, s), 7.53-7.60(1H, m), 8.30-8.36(1H, m), 8.77-8.80(1H, m), 8.96(1H, s), 9.11(1H, d, J=2 Hz), 11.5(1H, s)

ESI/MS: 413$[M+H]^+$, 435$[M+Na]^+$

IR (KBr): 3473, 2989, 1695, 1664, 1589, 1479, 1440 cm^{-1}

mp: 163-167°C (aq-EtOH)

Example 176

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (122.8 mg) was dissolved in dichloromethane (10 ml). To the solution were added pivaloyl chloride (96.5 mg) and diisopropyl ethyl amine (207 mg) at 25°C. The solution was stirred for 2 hours, and stood overnight. Concentration of the above reaction mixture gave oily residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was separated, and washed with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was pulverized with diisoprppyl ether (10 ml) to give N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2,2-dimethylpropanamide (142 mg).

^{1}H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.6 Hz), 1.25(9H, s), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.36(1H, d, J=9.6 Hz), 7.44(5H, s), 8.88(1H, s), 10.3(1H, s)

ESI/MS: 392$[M+H]^+$, 414$[M+Na]^+$

IR (KBr): 3253, 2973, 1706, 1654, 1571, 1482, 1446 cm^{-1}

mp: 138-141°C (IPE)

Example 177

2,2,2-trichloroethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylcarbamate was prepared according to a similar manner to that of Example 176.

^{1}H NMR (DMSO-d_6, δ): 1.05(6H, d, J=6.6 Hz), 4.94(2H, s), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.35(1H, d, J=9.6 Hz), 7.44(5H, s), 8.88(1H, s), 11.2(1H, s),
ESI/MS: 482$[M+H]^+$, 504$[M+Na]^+$
IR(KBr): 3253, 2973, 1745, 1654, 1571, 1482, 1446 cm^{-1}
mp: 158-162°C (IPE)

Example 178

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (61.4 mg) was dissolved in dichloromethane (10 ml). To the solution were added benzoyl chloride (56.2 mg) and diisopropyl ethyl amine (103 mg) at 25°C. The solution was stirred for 5 hours. Concentration of the above reaction mixture gave oily residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was separated, and washed with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was purified with column chromatography on silica gel to give N-benzoyl-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide, which was crystallized from 90%-aqeous ethanol (59.5mg).
^{1}H NMR (DMSO-d_6, δ): 1.04(6H, d, J=6.0 Hz), 5.01(1H, m), 7.04-7.05(2H, m), 7.29-7.40(4H, m), 7.49-7.70(6H, m), 7.83-7.87(4H, m), 8.99(1H, s)
ESI/MS: 516$[M+H]^+$, 538$[M+Na]^+$
IR (KBr): 3255, 1655, 1570, 1475, 1440 cm^{-1}
mp: 121-125°C (aq-EtOH)

Example 179

4-Fluoro-N-(4-fluorobenzoyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 178.
^{1}H NMR (DMSO-d_6, δ): 1.00(6H, d, J=6.6 Hz), 5.02(1H, m), 6.87(1H,

d, J=9.6 Hz), 7.10-7.15(2H, m), 7.32-7.42(8H, m), 7.90-7.98(4H, m), 9.00(1H, s)

ESI/MS: 552$[M+H]^+$, 574$[M+Na]^+$

IR (KBr): 3255, 1665, 1565, 1470, 1445 cm^{-1}

mp: 148-151°C (aq-EtOH)

Example 180

4-Chloro-N-(4-chlorobenzoyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO-d_6, δ): 1.00(6H, d, J=6.6 Hz), 5.01(1H, m), 6.81(1H, d, J=9.8 Hz), 7.10-7.15(2H, m), 7.32-7.42(3H, m), 7.51(4H, d, J=8.6 Hz), 7.87(4H, d, J=8.6 Hz), 9.00(1H, s)

ESI/MS: 584, 586$[M+H]^+$, 606, 608$[M+Na]^+$

IR (KBr): 3255, 1670, 1570, 1470, 1440 cm^{-1}

mp: 110°C (aq-EtOH)

Example 181

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methoxy-N-(4-methoxybenzoyl) benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO-d_6, δ): 0.99(6H, d, J=6.6 Hz), 3.82(6H, s), 5.02(1H, m), 6.91(1H, d, J=9.6 Hz), 7.05(4H, d, J=9.0 Hz), 7.12-7.16(2H, m), 7.34-7.41(4H, m), 7.80(4H, d, J=9.0 Hz), 8.96(1H, s),

ESI/MS: 576$[M+H]^+$, 598$[M+Na]^+$

IR (KBr): 3265, 1672, 1575, 1465, 1440 cm^{-1}

mp: 171-174°C (EtOH)

Example 182

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methyl-N-(4-methylbenzoyl) benzamide was prepared according to a similar manner to that of Example 178.

^{1}H NMR (DMSO-d_6, δ): 1.00(6H, d, J=6.6 Hz), 2.30(6H, s), 5.02(1H, m), 6.91(1H, d, J=9.6 Hz), 7.01-7.39(10H, m), 7.72-7.88(4H, m), 8.97(1H, s)

ESI/MS: 544$[M+H]^+$, 566$[M+Na]^+$

IR (KBr): 3265, 1675, 1570, 1470, 1445 cm^{-1}

mp: 159°C (aq-EtOH)

Example 183

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-(trifluoromethyl)-N-[4-(trifluoromethyl)benzoyl]benzamide was prepared according to a similar manner to that of Example 178.

^{1}H NMR (DMSO-d_6, δ): 0.95(6H, d, J=6.6 Hz), 5.00(1H, m), 6.93(1H, d, J=9.6 Hz), 7.01-7.05(2H, m), 7.30-7.44(4H, m), 8.09(4H, d, J=8.4 Hz), 9.03(1H, s),

ESI/MS: 652$[M+H]^+$, 674$[M+Na]^+$

IR (KBr): 3265, 1674, 1564, 1475, 1440 cm^{-1}

mp: 159°C (aq-EtOH)

Example 184

Dimethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylimidodicarbonate was prepared according to a similar manner to that of Example 178.

^{1}H NMR (DMSO-d_6, δ): 1.01(6H, d, J=6.6 Hz), 3.80(6H, s), 5.04(1H, m), 6.97(1H, d, J=9.6 Hz), 7.48(5H, s), 7.52(1H, d, J=9.6 Hz), 9.12(1H, s)

ESI/MS: 424$[M+H]^+$, 446$[M+Na]^+$

IR (KBr): 3265, 1694, 1550, 1460, 1440 cm^{-1}

mp: 216°C (aq-EtOH)

Example 185

To 1M-borontribromide solution in methylene chloride (70 ml) was added 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (4.72 g) at 5-10°C. The reaction mixture was stirred at room temperature for 2 hours. The mixture

was cooled in ice bath. To the cooled solution was added water. Organic layer was separated and concentrated in vacuo to give oily residue. To the residue was added the above separated aqueous layer. PH of the aqueous solution was adjusted to 6-7 with 10%-NaOH aqueous solution. White crystals were precipitated. The suspension was stirred at room temperature for 2 hours, at 0-5°C for 1 hour, and stood in the refrigerator overnight. The crystals were collected by filtration and dried in vacuo at 35-40°C, to give

6-[2-amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (4.45g).

^{1}H NMR (DMSO-d_6, δ): 1.17(6H, d, J=6.8 Hz), 5.06-5.12(1H, m), 6.74(2H, d, J=8.6 Hz), 6.77(1H, d, J=9.6 Hz), 6.95(2H, s), 7.03(1H, d, J=9.6 Hz), 7.20(2H, d, J=8.6 Hz), 8.35(1H, s), 9.80(1H, brs)

ESI/MS: 342$[M+H]^+$, 346$[M+Na]^+$

IR (KBr): 3149, 1652, 1583, 1479, 1407 cm^{-1}

mp: 246°C (H_2O)

Example 186

6-[2-Amino-4-(2-hydroxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

^{1}H NMR (DMSO-d_6, δ): 1.11(6H, d, J=6.6 Hz), 5.03-5.10(1H, m), 6.70-6.80(4H, m), 6.99(2H, brs), 7.08-7.20(2H, m), 8.42(1H, s), 9.53(1H, s)

ESI/MS: 342$[M+H]^+$, 346$[M+Na]^+$

IR (KBr): 3166, 1656, 1573, 1500, 1286 cm^{-1}

mp: 241°C (H_2O)

Example 187

6-[2-Amino-4-(3-hydroxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

^{1}H NMR (DMSO-d_6, δ): 0.98(6H, d, J=6.6 Hz), 4.95-5.01(1H, m), 6.72-6.89(3H, m), 6.99(2H, brs), 7.14-7.30(3H, m), 8.40(1H, s), 9.72(1H, s)

ESI/MS: 342$[M+H]^+$, 346$[M+Na]^+$

IR (KBr): 3181, 1654, 1581, 1484 cm^{-1}

mp: 204°C (H_2O)

Example 188

6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (97 mg) was dissolved in N,N-dimethylformaide (5 ml). To the solution were add ethyl bromide (36 mg) and potassium tert-butoxide (36.9 mg) at 25°C. The reaction mixture was stirred for 15 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and washed with brine. The aqueous layer was combined and extracted with ethyl acetate. The organic layer was combined and passed through the diatomaceous earth column. Evaporation of solvent at reduced pressure gave a residue. The residue was purified with column chromatography on silica gel (methanol: chloroform 5:95 - 10:90) to give 6-[2-amino-4-(4-ethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone, which was crystallized from 90% aq-ethanol (27.5 mg)

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6 Hz), 1.31(3H, t, J=7.0 Hz), 4.02(2H, q, J=7.0 Hz), 5.01-5.14(1H, m), 6.73(1H, d, J=9.6 Hz), 6.92(2H, d, J=8.8 Hz), 7.05(2H, s), 7.25(1H, d, J=9.6 Hz), 8.38(1H, s)

ESI/MS: 352$[M+H]^+$, 374$[M+Na]^+$

IR (KBr): 3374, 1645, 1585, 1405 cm^{-1}

mp: 204°C (aq-EtOH)

Example 189

6-[2-Amino-4-(2-ethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.93(6H, brs), 1.00(3H, t), 3.7(2H, brs), 4.92-4.99(1H, m), 6.80(1H, d, J=9.6 Hz), 6.97(2H, brs), 6.88-7.08(2H, m), 7.25(1H, d, J=9.6 Hz), 7.29-7.43(2H, m), 8.43(1H, s)

ESI/MS: 352$[M+H]^+$, 374$[M+Na]^+$

IR (KBr): 3193, 1641, 1575, 1482 cm^{-1}

mp: 185°C (aq-EtOH)

Example 190

6-[2-Amino-4-(3-ethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.08(6H, d, J=6.6 Hz), 1.26(3H, t, J=7.0 Hz), 3.93(2H, q, J=7.0 Hz), 5.02-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.85-6.96(3H, m), 7.06(2H, s), 7.14(1H, d, J=9.6 Hz), 7.27(1H, t, J=8.0 Hz), 8.44(1H, s)

ESI/MS: 352$[M+H]^+$, 374$[M+Na]^+$

IR (KBr): 3307, 1620, 1585, 1482 cm^{-1}

mp: 142°C (aq-EtOH)

Example 191

6-[2-Amino-4-(4-propoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.96(3H, t, J=7.4 Hz), 1.14(6H, d, J=6.6 Hz), 1.66-1.77(2H, m), 3.93(2H, d, J=6.6 Hz), 5.02-5.12(1H, m), 6.79(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.30(2H, d, J=8.8 Hz), 8.34(1H, s)

ESI/MS: 366$[M+H]^+$

IR (KBr): 3376, 1641, 1585, 1482 cm^{-1}

mp: 175°C (aq-EtOH)

Example 192

6-[2-Amino-4-(2-propoxyphenyl)-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.72(3H, t), 0.95-1.04(6H, m), 1.34-1.43(2H, m), 3.57-3.61(2H, m), 4.92-4.99(1H, m), 6.78(1H, d, J=9.6 Hz), 6.92(1H, d, J=8.4 Hz), 6.98(2H, s), 7.03(2H, m, J=t Hz), 7.22(1H, d, J=9.6 Hz), 7.31-7.40(2H, m), 8.46(1H, s)

ESI/MS: 366[M+H]$^+$

IR (KBr): 3421, 1648, 1573, 1452 cm^{-1}

mp: 145°C (aq-EtOH)

Example 193

6-[2-Amino-4-(3-propoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.92(3H, t, J=7.4 Hz), 1.08(6H, d, J=6.6 Hz), 1.60-1.67(2H, m), 3.83(2H, t, J=7.4 Hz), 5.05(1H, m), 6.80(1H, d, J=9.6 Hz), 6.84-6.91(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.24(1H, t, J=7.6 Hz), 8.44(1H, s)

ESI/MS: 366[M+H]$^+$, 388[M+Na]$^+$

IR (KBr): 3194, 1660, 1575, 1484 cm^{-1}

mp: 122°C (aq-EtOH)

Example 194

6-[2-Amino-4-(4-isopropoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.12(6H, d, J=6.6 Hz), 1.25(6H, d, J=6.0 Hz), 4.57-4.69(1H, m), 5.01-5.14(1H, m), 6.80(1H, d, J=9.6 Hz), 6.91(2H, d, J=8.8 Hz), 7.00(2H, s), 7.12(1H, d, J=9.6 Hz), 7.28(2H, d, J=8.8 Hz), 8.38(1H, s)

APCI/MS: 366[M+H]$^+$

IR (KBr): 3180, 1643, 1569, 1481 cm^{-1}

mp: 164°C (aq-EtOH)

Example 195

6-[2-Amino-4-(2-isopropoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinonee was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.72(3H, t), 0.95-1.04(6H, m), 1.34-1.43(2H, m), 3.57-3.61(2H, m), 4.92-4.99(1H, m), 6.78(1H, d, J=9.6 Hz), 6.92(1H, d, J=8.4 Hz), 6.98(2H, s), 7.03(2H, m, J=t Hz), 7.22(1H, d, J=9.6 Hz), 7.31-7.40(2H, m), 8.46(1H, s)

APCI/MS: 366$[M+H]^+$

IR (KBr): 3421, 1648, 1573, 1452 cm^{-1}

mp: 202°C (aq-EtOH)

Example 196

6-[2-Amino-4-(3-isopropoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.03(6H, t, J=7.4 Hz), 1.17(6H, d, J=6.6 Hz), 4.44-4.50(1H, m), 5.01-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.81-6.94(3H, m), 7.06(2H, s), 7.16(1H, d, J=9.6 Hz), 7.24-7.31(2H, m), 8.44(1H, s)

APCI/MS: 366$[M+H]^+$

IR (KBr): 3191, 1648, 1573, 1492 cm^{-1}

mp: 143°C (aq-EtOH)

Example 197

6-[2-Amino-4-(4-butoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.92(3H, t, J=7.2 Hz), 1.14(6H, d, J=6.6 Hz), 1.36-1.47(2H, m), 1.61-1.71(2H, m), 3.97(2H, t, J=6.4 Hz), 5.04-5.11(1H, m), 6.77(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, s), 7.03(1H, d, J=9.6 Hz), 7.29(2H, d, J=8.8 Hz), 8.38(1H, s)

APCI/MS: 380$[M+H]^+$

IR (KBr): 3384, 1641, 1583, 1484 cm^{-1}

mp: 143°C (aq-EtOH)

Example 198

6-[2-Amino-4-(2-butoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.77(3H, t, J=7.6 Hz), 0.94-1.04(6H, m), 1.11-1.19(2H, m), 1.32-1.38(2H, m), 3.66(2H, m), 4.92-4.99(1H, m), 6.79(1H, d, J=9.6 Hz), 6.92(2H, d, J=8.4 Hz), 6.98(2H, s), 7.04(1H, t, J=7.2 Hz), 7.22(1H, d, J=9.6 Hz), 7.31-7.40(2H, m), 8.45(1H, s)

APCI/MS: 380[M+H]$^+$

IR (KBr): 3394, 1664, 1581, 1484 cm^{-1}

mp: 149°C (aq-EtOH)

Example 199

6-[2-Amino-4-(3-butoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.89(3H, t, J=7.2 Hz), 1.04(6H, t, J=6.6 Hz), 1.28-1.46(2H, m), 1.56-1.69(2H, m), 3.86(2H, t, J=6.4 Hz), 4.99-5.11(1H, m), 6.80(1H, d, J=9.6 Hz), 6.84-6.99(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.28(1H, t, J=8 Hz), 8.43(1H, s)

APCI/MS: 380[M+H]$^+$

IR (KBr): 3313, 1646, 1577, 1471 cm^{-1}

mp: 130°C (aq-EtOH)

Example 200

6-[2-Amino-4-(4-isobutoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.96(6H, d, J=6.6 Hz), 1.14(6H, d, J=6.6 Hz), 1.96(1H, m), 3.75(2H, t, J=6.4 Hz), 5.04-5.11(1H, m), 6.78(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, sd),

7.07(1H, d, J=9.6 Hz), 7.30(2H, d, J=8.8 Hz), 8.38(1H, s)
APCI/MS: 380[M+H]$^+$
IR (KBr): 3386, 1639, 1585, 1484 cm^{-1}
mp: 166°C (aq-EtOH)

Example 201

6-[2-Amino-4-(2-isobutoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.
^{1}H NMR (DMSO-d_6, δ): 0.72(6H, d, J=6.8 Hz), 0.98-1.04(6H, m), 1.62-1.68(1H, m), 3.46(2H, d, J=6.8 Hz), 4.93-4.99(1H, m), 6.77(1H, d, J=9.6 Hz), 6.93(1H, d, J=8.0 Hz), 6.98(2H, s), 7.03(1H, t, J=7.2 Hz), 7.20(1H, d, J=9.6 Hz), 7.31-7.40(2H, m), 8.49(1H, s)
APCI/MS: 380[M+H]$^+$
IR (KBr): 3322, 1650, 1590, 1492 cm^{-1}
mp: 189°C (aq-EtOH)

Example 202

6-[2-Amino-4-(3-isobutoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.
^{1}H NMR (DMSO-d_6, δ): 0.91(6H, d, J=6.6 Hz), 1.08(6H, d, J=6.6 Hz), 1.86-1.99(2H, m), 3.63(2H, d, J=6.6 Hz), 5.02-5.09(1H, m), 6.80(1H, d, J=9.6Hz), 6.84-6.97(3H, m), 7.07(2H, s), 7.13(1H, d, J=9.6 Hz), 7.28(1H, t, J=7.8 Hz), 8.44(1H, s)
APCI/MS: 380[M+H]$^+$
IR (KBr): 3315, 1666, 1573, 1486 cm^{-1}
mp: 137°C (aq-EtOH)

Example 203

6-{2-Amino-4-[4-(isopentyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.
^{1}H NMR (DMSO-d_6, δ): 0.92(6H, d, J=6.4 Hz), 1.13(6H, d, J=6.6

Hz), 1.55-1.64(2H, m), 1.7-1.80(1H, m), 3.99(2H, t, J=6.4 Hz), 5.05-5.11(1H, m), 6.79(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.29(2H, d, J=8.8 Hz), 8.38(1H, s)

ESI/MS: 394$[M+H]^+$, 416$[M+Na]^+$

IR (KBr): 3383, 1640, 1586, 1480 cm^{-1}

mp: 164°C (aq-EtOH)

Example 204

6-{2-Amino-4-[2-(isopentyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO-d_6, δ): 0.76(6H, d, J=6.6 Hz), 0.96-1.05(6H, m), 1.21-1.31(2H, m), 1.40-1.50(1H, m), 3.67(2H, m), 4.92-4.99(1H, m), 6.79(1H, d, J=9.6Hz), 6.92-7.08(2H, m), 6.96(2H, s), 7.24(1H, d, J=9.6 Hz), 7.29-7.41(2H, m), 8.46(1H, s)

ESI/MS: 394$[M+H]^+$, 416$[M+Na]^+$

IR (KBr): 3325, 1655, 1585, 1488 cm^{-1}

mp: 155°C (aq-EtOH)

Example 205

6-{2-Amino-4-[3-(isopentyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO-d_6, δ): 0.89(6H, d, J=6.4 Hz), 1.08(6H, d, J=6.6 Hz), 1.49-1.59(2H, m), 1.65-1.75(1H, m), 3.88(2H, d, J=6.4 Hz), 5.01-5.08(1H, m), 6.79(1H, d, J=9.6 Hz), 6.83-6.96(3H, m), 7.09(2H, s), 7.14(1H, d, J=9.6 Hz), 7.28(1H, t, J=8.0 Hz), 8.44(1H, s)

ESI/MS: 394$[M+H]^+$, 416$[M+Na]^+$

IR (KBr): 3310, 1656, 1570, 1480 cm^{-1}

mp: 97°C (aq-EtOH)

Example 206

6-{2-Amino-4-[4-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a

similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.87(3H, d, J=7.6 Hz), 1.14(6H, d, J=6.6 Hz), 1.25-1.63(6H, m), 3.96(2H, t, J=6.4 Hz), 5.01-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.29(2H, d, J=8.8 Hz), 8.38(1H, s)

ESI/MS: 408$[M+H]^+$, 430$[M+Na]^+$

IR (KBr): 3370, 1660, 1570, 1485 cm^{-1}

mp: 184°C (aq-EtOH)

Example 207

6-{2-Amino-4-[2-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.8(3H, d, J=6.8 Hz), 0.95(6H, m), 1.14-1.39(8H, m), 3.65(2H, m), 4.92-4.98(1H, m), 6.78(1H, d, J=9.6 Hz), 6.90-7.07(4H, m), 6.96(2H, s), 7.23(1H, d, J=9.6 Hz), 7.29-7.41(2H, m), 8.45(1H, s)

ESI/MS: 408$[M+H]^+$, 430$[M+Na]^+$

IR (KBr): 3325, 1655, 1585, 1488 cm^{-1}

mp: 92°C (aq-EtOH)

Example 208

6-{2-Amino-4-[3-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.87(3H, t, J=6.8 Hz), 1.04(6H, d, J=8.4 Hz), 1.29-1.38(6H, m), 1.57-1.67(2H, m), 3.85(2H, t, J=6.4 Hz), 4.98-5.12(1H, m), 6.79(1H, d, J=9.6 Hz), 6.84-6.96(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6Hz), 7.24-7.32(1H, m), 8.44(1H, s)

ESI/MS: 408$[M+H]^+$, 430$[M+Na]^+$

IR (KBr): 3330, 1660, 1580, 1485 cm^{-1}

mp: 121°C (aq-EtOH)

Example 209

6-{2-Amino-4-[4-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6 Hz), 4.15-4.17(2H, m), 4.30-4.34(2H, m), 5.05-5.11(1H, m), 6.79(1H, d, J=9.6 Hz), 6.98(2H, d, J=8.8 Hz), 7.06(2H, s), 7.08(1H, d, J=9.6 Hz), 7.32(2H, d, J=8.8 Hz), 8.39(1H, s)

ESI/MS: 370$[M+H]^+$, 392$[M+Na]^+$

IR (KBr): 3178, 1635, 1585, 1482 cm^{-1}

mp: 200°C (aq-EtOH)

Example 210

6-{2-Amino-4-[2-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 0.93-1.05(6H, m), 3.60-4.00(2H, m), 4.30-4.57(2H, m), 4.91-4.97(1H, m), 6.78(1H, d, J=9.6 Hz), 6.93-7.43(4H, m), 7.05(2H, s), 7.22(1H, d, J=9.6 Hz), 8.45(1H, s)

ESI/MS: 370$[M+H]^+$, 392$[M+Na]^+$

IR (KBr): 3189, 1658, 1585, 1479 cm^{-1}

mp: 171°C (aq-EtOH)

Example 211

6-{2-Amino-4-[3-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.07(6H, d, J=6.6 Hz), 4.07-4.10(1H, m), 4.22-4.26(1H, m), 4.56-4.60(1H, m), 4.80-4.84(1H, m), 5.02-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.86-7.33(4H, m), 7.08(2H, s), 7.17(1H, d, J=9.6 Hz), 8.45(1H, s)

ESI/MS: 370$[M+H]^+$, 392$[M+Na]^+$

IR (KBr): 3183, 1641, 1575, 1487 cm^{-1}

mp: 123°C (aq-EtOH)

Example 212

6-{2-Amino-4-[4-(2-methoxyethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6 Hz), 3.30(3H, s), 3.62(2H, m), 4.10(2H, m), 5.05-5.11(1H, m), 6.78(1H, d, J=9.6 Hz), 6.95(2H, d, J=8.8 Hz), 7.01(2H, s), 7.07(1H, d, J=9.6 Hz), 7.30(2H, d, J=8.8 Hz), 8.39(1H, s)

ESI/MS: 382$[M+H]^+$, 404$[M+Na]^+$

IR (KBr): 3328, 1666, 1563, 1475 cm^{-1}

mp: 147°C (aq-EtOH)

Example 213

6-{2-Amino-4-[3-(2-methoxyethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.01-1.09(6H, m), 3.28(3H, s), 3.57-3.61(2H, m), 3.98-4.02(2H, m), 5.01-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.86-6.99(3H, m), 7.08(2H, s), 7.15(1H, d, J=9.6 Hz), 7.24-7.32(1H, m), 8.44(1H, s)

ESI/MS: 382$[M+H]^+$, 404$[M+Na]^+$

IR (KBr): 2960, 1671, 1573, 1471 cm^{-1}

Example 214

6-{2-Amino-4-[4-(3-fluoropropoxy)phenyl]-5-pyrimidinyl-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6 Hz), 2.00-2.19(2H, m), 4.08(2H, t, J=6.2 Hz), 4.48(1H, t, J=6.0 Hz), 4.71(1H, t, J=6.2 Hz), 5.01-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.96(2H, d, J=8.8 Hz), 7.01(2H, s), 7.08(1H, d, J=9.6 Hz), 7.31(2H, d, J=8.8 Hz), 8.39(1H, s)

ESI/MS: 384$[M+H]^+$, 406$[M+Na]^+$

IR (KBr): 3187, 1656, 1587, 1469 cm^{-1}

mp: 179°C (aq-EtOH)

Example 215

6-{2-Amino-4-[2-(3-fluoropropoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO-d_6, δ): 0.94(6H, brs), 1.61-1.88(2H, m), 3.78(2H, m), 4.21(1H, t, J=6.0 Hz), 4.44(1H, t, J=6.0 Hz), 4.92-4.99(1H, m), 6.78(1H, d, J=9.6Hz), 6.89(2H, s), 6.94-7.09(2H, m), 7.24(1H, d, J=9.6 Hz), 7.31-7.41(2H, m), 8.46(1H, s)

ESI/MS: 384$[M+H]^+$, 406$[M+Na]^+$

IR (KBr): 3156, 1635, 1579, 1486 cm^{-1}

mp: 200°C (aq-EtOH)

Example 216

6-{2-Amino-4-[3-(3-fluoropropoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO-d_6, δ): 1.07(6H, d, J=6.6 Hz), 1.95-2.14(2H, m), 4.00(2H, t, J=6.0 Hz), 4.44(1H, t, J=6.0 Hz), 4.68(1H, t, J=6.0 Hz), 5.01-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.86-6.99(3H, m), 7.07(2H, s), 7.15(1H, d, J=9.6 Hz), 7.29(1H, t, J=5.8 Hz), 8.44(1H, s)

ESI/MS: 384$[M+H]^+$, 406$[M+Na]^+$

IR (KBr): 3191, 1658, 1575, 1485 cm^{-1}

mp: 123°C (aq-EtOH)

Example 217

6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (97 mg) was dissolved in N,N-dimethylformaide (5 ml). To the solution were add 2-dimethylaminoethyl chloride hydrochloride (47.5 mg) and potassium tert-butoxide (73.9 mg) at 25°C. The reaction mixture was stirred for 15 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate.

The organic layer was separated and washed with brine. The aqueous layer was combined and extracted with ethyl acetate. The organic layer was combined and passed through the diatomaceous earth column. Evaporation of solvent under reduced pressure gave a residue. The residue was purified with column chromatography on silica gel (methanol:chloroform 10:90 - 20:80) to give 6-(2-amino-4-{4-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone, which was crystallized from 90% aq-ethanol (36.3 mg).

^{1}H NMR (DMSO-d_6, δ): 1.13(6H, d, J=6.6 Hz), 2.20(6H, s), 2.60(2H, t, J=6.0 Hz), 4.05(2H, t, J=6.0 Hz), 5.05-5.11(1H, m), 6.78(1H, d, J=9.6 Hz), 6.94(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.30(2H, d, J=8.8 Hz), 8.38(1H, s)

ESI/MS: 395$[M+H]^+$, 417$[M+Na]^+$

IR (KBr): 3421, 1652, 1587, 1484 cm^{-1}

mp: 162°C (aq-EtOH)

Example 218

6-(2-Amino-4-{2-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^{1}H NMR (DMSO-d_6, δ): 0.95(6H, brs), 2.23(6H, s), 2.28(2H, t, J=5.6 Hz), 3.73(2H, brs), 5.05-5.11(1H, m), 6.80(1H, d, J=9.6 Hz), 6.96-7.08(2H, m), 7.00(2H, s), 7.27(1H, d, J=9.6 Hz), 7.33-7.41(2H, d), 8.45(1H, s)

ESI/MS: 395$[M+H]^+$, 417$[M+Na]^+$

IR (KBr): 3160, 1664, 1573, 1457 cm^{-1}

mp: 198°C (aq-EtOH)

Example 219

6-(2-Amino-4-{3-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^{1}H NMR (DMSO-d_6, δ): 1.08(6H, d, J=6.6 Hz), 2.16(6H, s), 2.55(2H, t, J=5.6 Hz), 3.94(2H, t, J=5.6 Hz), 5.01-5.08(1H, m), 6.80(1H, d, J=9.6 Hz), 6.85-6.98(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.24-7.32(1H, d), 8.44(1H, s)

ESI/MS: 395$[M+H]^+$, 417$[M+Na]^+$

IR (KBr): 3421, 1635, 1592, 1484 cm^{-1}

mp: 111°C (aq-EtOH)

Example 220

6-(2-Amino-4-{4-[2-(4-morpholinyl)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^{1}H NMR (DMSO-d_6, δ): 1.14(6H, d, J=6.6 Hz), 2.45(4H, t, J=4.8 Hz), 2.67(2H, t, J=5.6 Hz), 3.56(4H, t, J=4.8 Hz), 4.09(2H, t, J=5.6 Hz), 5.05-5.11(1H, m), 6.79(1H, d, J=9.6 Hz), 6.95(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.30(2H, d, J=8.8 Hz), 8.38(1H, s)

ESI/MS: 437$[M+H]^+$, 459$[M+Na]^+$

IR (KBr): 3309, 1662, 1589, 1479 cm^{-1}

mp: 161°C (aq-EtOH)

Example 221

6-(2-Amino-4-{2-[2-(4-morpholinyl)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^{1}H NMR (DMSO-d_6, δ): 1.02(6H, brs), 2.26(4H, t, J=4.4 Hz), 2.36(2H, t, J=6.0 Hz), 3.45(4H, t, J=4.4 Hz), 3.75(2H,), 5.05-5.11(1H, m), 6.80(1H, d, J=9.6Hz), 6.93-7.08(2H, m), 6.98(2H, s), 7.29(1H, d, J=9.6 Hz), 7.29-7.39(2H, m), 8.45(1H, s)

ESI/MS: 437$[M+H]^+$, 459$[M+Na]^+$

IR (KBr): 3334, 1648, 1575, 1479 cm^{-1}

mp: 115°C (aq-EtOH)

Example 222

6-(2-Amino-4-{3-[2-(4-morpholinyl)ethoxy]phenyl}-

5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^{1}H NMR (DMSO-d_6, δ): 1.02-1.10(6H, m), 2.42(4H, t, J=4.6 Hz), 2.62(2H, t, J=5.8 Hz), 3.55(4H, t, J=4.6 Hz), 3.98(2H, t, J=5.8 Hz), 5.05-5.11(1H, m), 6.80(1H, d, J=9.6 Hz), 6.85-6.98(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6Hz), 7.24-7.32(1H, m), 8.43(1H, s)

ESI/MS: 437$[M+H]^+$, 459$[M+Na]^+$

IR (KBr): 3309, 1650, 1573, 1475 cm-1

mp: 68°C (aq-EtOH)

Example 223

6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

^{1}H NMR (DMSO-d_6, δ): 3.68(3H, s), 6.65-6.88(4H, m), 6.97(2H, brs), 7.26(2H, d, J=8.6 Hz), 8.33(1H, s), 9.87(1H, brs)

ESI/MS: 296$[M+H]^+$, 318$[M+Na]^+$

IR (KBr): 3180, 1641, 1573, 1481, 1411 cm^{-1}

mp: 250°C (H_2O)

Example 224

6-[2-Amino-4-(2-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

^{1}H NMR (DMSO-d_6, δ): 3.58(3H, s), 6.71(1H, d, J=9.6 Hz), 6.76-6.88(2H, m), 6.95(1H, d, J=9.6 Hz), 7.05(2H, brs), 7.21-7.28(2H, m), 8.41(1H, s), 10.0(1H, s)

ESI/MS: 296$[M+H]^+$, 318$[M+Na]^+$

IR (KBr): 3180, 1646, 1579, 1496, 1440 cm^{-1}

mp: 260°C (H_2O)

Example 225

6-[2-Amino-4-(3-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner

to that of Example 185.

^{1}H NMR (DMSO-d_6, δ): 3.68(3H, s), 6.69-6.83(5H, m), 7.06(2H, brs), 7.18(1H, t, J=7.8 Hz), 8.39(1H, s), 9.59(1H, s)

ESI/MS: 296$[M+H]^+$, 318$[M+Na]^+$

mp: 285°C (H_2O)

Example 226

6-[2-Amino-4-(4-bromophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.74(1H, d, J=9.8 Hz), 6.98(1H, d, J=9.8 Hz), 7.19(2H, s), 7.34(2H, d, J=8.4 Hz), 7.61(2H, d, J=8.4 Hz), 8.40(1H, s), 13.1(1H, s)

ESI/MS: 342, 344$[M+H]^+$

IR (KBr): 3316, 1683, 1583, 1473 cm^{-1}

Example 227

6-[2-Amino-4-(3-bromophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.75(1H, d, J=10.0 Hz), 7.03(1H, d, J=9.6 Hz), 7.15(2H, s), 7.27-7.38(2H, m), 7.61-7.66(2H, m), 8.42(1H, s)

ESI/MS: 366, 368$[M+Na]^+$

IR (KBr): 3320, 1625, 1583, 1471 cm^{-1}

Example 228

6-[2-Amino-4-(2,6-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.80(1H, d, J=9.6 Hz), 7.10-7.24(3H, m), 7.21(1H, s), 7.30(1H, d, J=9.6 Hz), 7.48-7.55(1H, m), 8.55(1H, s), 12.95(1H, s)

ESI/MS: 324$[M+Na]^+$

Example 229

6-[2-Amino-4-(3,5-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.78(1H, d, J=9.8 Hz), 7.03-7.11(3H, m), 7.18(2H, s), 7.30-7.41(1H, m), 8.45(1H, s), 13.1(1H, s)

ESI/MS: 302$[M+H]^+$, 324$[M+Na]^+$

IR (KBr): 3342, 1623, 1585, 1490 cm^{-1}

Example 230

6-[2-Amino-4-(2,6-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.78(1H, d, J=9.8 Hz), 7.19-7.24(3H, m), 7.40-7.55(3H, m), 8.58(1H, s), 12.96(1H, s)

ESI/MS: 356, 358$[M+Na]^+$

IR (KBr): 3305, 1654, 1583, 1484 cm^{-1}

Example 231

6-[2-Amino-4-(2,6-dimethylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 1.96(6H, s), 6.59(1H, d, J=9.8 Hz), 6.72(1H, d, J=9.8 Hz), 7.04-7.07(4H, m), 7.15-7.22(1H, m), 8.48(1H, s), 13.04(1H, s)

ESI/MS: 294$[M+H]^+$, 316$[M+Na]^+$

IR (KBr): 3156, 1679, 1575, 1475 cm^{-1}

Example 232

6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 6.51-6.52(1H, m), 6.84(1H, d, J=9.8 Hz), 6.94(2H, s), 7.26(1H, d, J=9.8 Hz), 7.71-7.78(2H, m), 8.26(1H, s), 13.1(1H, s)

ESI/MS: 256$[M+H]^+$, 278$[M+Na]^+$

IR (KBr): 3187, 1658, 1581, 1490 cm^{-1}

Example 233

6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 6.76(1H, dd, J=9.6,2.2 Hz), 6.98(2H, s), 7.03(1H, d, J=9.6 Hz), 7.13-7.16(1H, m), 7.55-7.59(1H, m), 7.62-7.64(1H, m), 8.31(1H, s), 13.11(1H, s)

ESI/MS: 272$[M+H]^+$, 294$[M+Na]^+$

IR (KBr): 3205, 1673, 1581, 1482 cm^{-1}

Example 234

6-[2-Amino-4-(2,6-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 3.60(6H, s), 6.60(1H, d, J=10.8 Hz), 6.66(2H, d, J=8.4 Hz), 6.84(1H, d, J=9.8 Hz), 6.96(2H, s), 7.33(1H, t, J=8.4 Hz), 8.35(1H, s), 12.95(1H, s)

ESI/MS: 326$[M+H]^+$, 340$[M+Na]^+$

IR (KBr): 3133, 1677, 1594, 1469 cm^{-1}

Example 235

6-[2-Amino-4-(4-bromophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 1.01(6H, d, J=6.6 Hz), 4.96-5.10(1H, m), 6.85(1H, d, J=9.6 Hz), 7.12(2H, s), 7.28(1H, d, J=9.6 Hz), 7.28(2H, d, J=8.8 Hz), 7.58(2H, d, J=8.8 Hz), 8.47(1H, s),

ESI/MS: 384, 386$[M+H]^+$,

IR (KBr): 3397, 1646, 1581, 1481 cm^{-1}

mp: 204°C (aq-EtOH)

Example 236

6-[2-Amino-4-(3-bromophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a

similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 0.99(6H, d, J=6.6 Hz), 4.96-5.09(1H, m), 6.87(1H, d, J=9.6 Hz), 7.16(2H, s), 7.25-7.34(2H, m), 7.35(2H, d, J=9.6 Hz), 7.55-7.61(2H, m), 8.49(1H, s),

ESI/MS: 384, 386$[M+H]^+$

IR (KBr): 3183, 1621, 1583, 1484 cm^{-1}

mp: 238-240°C (aq-EtOH)

Example 237

6-[2-Amino-4-(2,6-difluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 0.82(6H, d, J=6.6 Hz), 4.86-4.99(1H, m), 6.92(1H, d, J=9.6 Hz), 7.09-7.19(2H, m), 7.23(2H, s), 7.40-7.55(1H, m), 8.62(1H, s)

ESI/MS: 366$[M+Na]^+$

mp: 244°C (aq-EtOH)

Example 238

6-[2-Amino-4-(3,5-difluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 0.99(6H, d, J=6.6 Hz), 4.96-5.10(1H, m), 6.91(1H, d, J=9.6 Hz), 7.01-7.06(2H, m), 7.20(2H, s), 7.24-7.35(1H, m), 7.43(1H, d, J=9.6 Hz), 8.53(1H, s)

ESI/MS: 344$[M+H]^+$, 366$[M+Na]^+$

IR (KBr): 3421, 1635, 1583, 1490 cm^{-1}

mp: 234°C (aq-EtOH)

Example 239

6-[2-Amino-4-(2,6-dichlorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^{1}H NMR (DMSO-d_6, δ): 0.82(6H, d, J=6.6 Hz), 4.86-5.00(1H, m), 6.91(1H, d, J=9.6 Hz), 7.30-7.54(3H, m), 7.23(2H, s), 7.66(1H,

d, J=9.6 Hz), 8.67(1H, s)

ESI/MS: 376, 378$[M+H]^+$, 398, 400$[M+Na]^+$

IR (KBr): 3303, 1658, 1592, 1486 cm^{-1}

mp: 208°C (aq-EtOH)

Example 240

6-[2-Amino-4-(2,6-dimethylphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 0.92(6H, d, J=6.6 Hz), 1.94(6H, s), 4.97(1H, m), 6.78(1H, d, J=9.6 Hz), 7.00-7.17 (5H, m), 7.28(1H, d, J=9.6 Hz)

ESI/MS: 336$[M+H]^+$, 358$[M+Na]^+$, 693$[2M+Na]^+$

IR (KBr): 3340, 1652, 1583, 1486 cm^{-1}

mp: 212°C (aq-EtOH)

Example 241

6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 1.23(6H, d, J=6.6 Hz), 5.09-5.22(1H, m), 6.45(1H, s), 6.89(1H, d, J=9.6 Hz), 6.96(2H, s), 7.31(1H, d, J=9.6 Hz), 7.69-7.74(2H, m), 8.31(1H, s)

ESI/MS: 298$[M+H]^+$, 320$[M+Na]^+$

IR (KBr): 3160, 1650, 1591, 1489 cm^{-1}

mp: 216°C (aq-EtOH)

Example 242

6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 1.18(6H, d, J=6.6 Hz), 5.04-5.17(1H, m), 6.84(1H, d, J=9.6 Hz), 7.00(2H, s), 7.05-7.08(1H, m), 7.18(1H, d, J=9.6 Hz), 7.53-7.61(2H, m), 8.37(1H, s)

ESI/MS: 314$[M+H]^+$, 336$[M+Na]^+$

IR (KBr): 3189, 1675, 1581, 1482 cm^{-1}

mp: 234°C (aq-EtOH)

Example 243

6-[2-Amino-4-(2,6-dimethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 0.99(6H, d, J=6.6 Hz), 3.57(6H, s), 4.97(1H, m), 6.63(2H, d, J=8.4 Hz), 6.73(1H, d, J=9.6 Hz), 6.91(2H, s), 7.15(1H, d, J=9.6 Hz), 7.27(1H, t, J=8.4 Hz), 8.40(1H, s)

ESI/MS: 368$[M+H]^+$, 390$[M+Na]^+$

IR (KBr): 3409, 1648, 1581, 1486 cm^{-1}

mp: 260°C (aq-EtOH)

Example 244

6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 3.69(3H, s), 6.54(1H, d, J=9.6 Hz), 6.88(1H, d, J=9.6 Hz), 6.94(2H, s), 7.25(1H, d, J=9.6 Hz), 7.70-7.80(2H, m), 8.26(1H, s)

ESI/MS: 292$[M+Na]^+$

IR (KBr): 3153, 1664, 1583, 1492 cm^{-1}

mp: 241°C (aq-EtOH)

Example 245

6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO-d_6, δ): 3.69(3H, s), 6.80(1H, d, J=9.6 Hz), 7.04(2H, s), 7.04(1H, d, J=9.6 Hz), 7.17-7.20(1H, m), 7.55-7.66(2H, m), 8.31(1H, s)

ESI/MS: 286$[M+H]^+$, 308$[M+Na]^+$

IR (KBr): 3154, 1664, 1579, 1490 cm^{-1}

mp: 252°C (aq-EtOH)

Example 246

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone (60 mg) was dissolved in N,N-dimethylformamide (5 ml). To the solution were added 60%-sodium hydride (28 mg) and methyl iodide (101 mg) at 25°C. The reaction mixture was heated at 50°C and stirred for 20 hours. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and washed with brine, and dried over magnesium sulfate. Evaporation of solvent in vacuo gave a residue. The residue was purified with chromatography on silica gel (methanol:chloroform 5:95 - 10:90), to give 6-[4-(4-chlorophenyl)-2-(dimethylamino)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone, which was crystallized from diisopropyl ether (30mg).

^{1}H NMR (DMSO-d_6, δ): 3.21(6H, s), 3.68(3H, s), 6.76(1H, d, J=9.6 Hz), 6.91(1H, d, J=9.6 Hz), 7.40-7.50(4H, m), 8.45(1H, s)

ESI/MS: 342, 344$[M+H]^+$, 364, 366$[M+Na]^+$

IR (KBr): 3354, 1674, 1580, 1480 cm^{-1}

mp: 166°C (IPE)

Example 247

6-[2-(Dimethylamino)-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 246.

^{1}H NMR (DMSO-d_6, δ): 3.21(6H, s), 3.68(3H, s), 3.78(3H, s), 6.75(1H, d, J=9.6 Hz), 6.86(1H, d, J=9.6 Hz), 6.97(1H, d, J=8.8 Hz), 7.45(1H, d, J=8.8 Hz), 8.45(1H, s),

ESI/MS: 338$[M+H]^+$, 360$[M+Na]^+$

IR (KBr): 3354, 1653, 1563, 1485 cm^{-1}

mp: 165°C (IPE)

Example 248

6-[2-(Dimethylamino)-4-(3-fluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar

manner to that of Example 246.

^{1}H NMR (DMSO-d_6, δ): 3.21(6H, s), 3.68(3H, s), 6.75(1H, d, J=9.6 Hz), 6.93(1H, d, J=9.6 Hz), 7.16-7.45(3H, m), 8.45(1H, s)

ESI/MS: 326[M+H]$^+$, 348[M+Na]$^+$

IR (KBr): 3362, 1685, 1562, 1475 cm^{-1}

mp: 184°C (IPE)

Example 249

6-[2-(Dimethylamino)-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 246.

^{1}H NMR (DMSO-d_6, δ): 3.21(6H, s), 3.68(3H, s), 3.86(3H, s), 6.78(1H, d, J=9.6 Hz), 6.94(1H, d, J=9.6 Hz), 7.16-7.23(2H, m), 7.42(1H, d, J=14 Hz), 8.45(1H, s)

ESI/MS: 356[M+H]$^+$, 378[M+Na]$^+$

IR (KBr): 3274, 1685, 1564, 1480 cm^{-1}

mp: 158°C (IPE)

Example 250

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-(2-methoxy-1-methylethyl)-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 180-181°C (EtOAc)

^{1}H NMR (DMSO-d_6, δ): 1.00(3H, d, J=6.8 Hz), 3.16(3H, s), 3.19-3.44(2H, m), 5.11-5.21(1H, m), 6.79(1H, d, J=9.6 Hz), 7.08(2H, br s), 7.13(1H, d, J=9.6 Hz), 7.30-7.42(5H, m), 8.44(1H, s)

Elemental Analysis for $C_{18}H_{19}N_5O_2$

Calcd.: C,64.08; H,5.68; N,20.76

Found : C,64.23; H,5.67; N,20.84

ESI/MS: 360[M+Na]$^+$

Example 251

To a stirred solution of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-(2-methoxy-

1-methylethyl)-3(2H)-pyridazinone (195 mg) in dichloromethane (4 ml) was added boron tribromide (0.273 ml) under ice cooling and the mixture was allowed to stir at 0°C - room temperature for 3.5h. The mixture was poured into ice-water, neutralized with sat.NaHCO3 and extracted with chloroform (x2). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford 168 mg of crystals. The crude material was purified by silica-gel column chromatography (CHCl3-MeOH, 30:1) to give 129 mg of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-(2-hydroxy-1-methylethyl)-3(2H)-pyridazinone as colorless crystals.

mp: 222-223°C (90% EtOH)

^{1}H NMR (DMSO-d_6, δ): 0.99(3H, d, J=6.8 Hz), 3.28-3.45(1H, m), 3.47-3.57(1H, m), 4.72(1H, t, J=5.8 Hz), 4.93-5.03(1H, m), 6.77(1H, d, J=9.6 Hz), 7.06(2H, s), 7.05(1H, d, J=9.6 Hz), 7.34-7.42(5H, m), 8.45(1H, s).

Elemental Analysis for $C_{17}H_{17}N_5O_2$

Calcd.: C,63.15; H,5.30; N,21.66

Found : C,63.23; H,5.31; N,21.69

APCI/MS: 324$[M+H]^+$

Example 252

A mixture of 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (1.00 g), triethylamine hydrochloride (0.51 g) and phosphorous oxychloride (1.44 ml) was heated at 100-105°C for 3 hours. After cooling, the mixture was poured into ice-water, neutralized with saturated sodium hydrogen carbonate solution, extracted with chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (ethyl acetate) to give 6-(2-amino-4-chloro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (365 mg).

mp: 235-237°C (acetone)

IR (KBr): 3404, 3199, 1645, 1581, 1570 cm^{-1}

ESI/MS: 366 and 364 $[M+Na]^+$

^1H NMR($CDCl_3$, δ): 1.09(6H, d, J=6.60 Hz), 5.22(1H, 7-plet, J=6.60 Hz), 5.48(2H, br.s), 6.83(1H, d, J=9.52 Hz), 7.08(1H, d, J=9.52 Hz), 7.26-7.35(5H, m)

Example 253

To a mixture of 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (386 mg) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (56.9 mg) in tetrahydrofuran (10 ml) was dropwise added a 3 M solution of methyl magnesium bromide in tetrahydrofuran (1.7 ml) under an atmosphere of nitrogen. The mixture was stirred at atmosphere temperature for 20 hours and concentrated under reduced pressure to give a residue. The residue was dissolved in a mixture of aqueous ammonium chloride solution and chloroform. An organic layer was dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (ethyl acetate) to give 6-(2-amino-4-methyl-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (66 mg).

mp: 213-215°C (methanol)

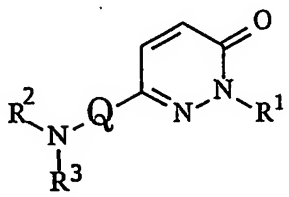
IR (KBr) : 3433, 3325, 3194, 1639, 1587, 1562 cm^{-1}

ESI/MS: 665 $[2M+Na]^+$, 344 $[M+Na]^+$, 322 $[M+H]^+$

^1H NMR($CDCl_3$, δ): 1.28(6H, d, J=6.62 Hz), 2.36(3H, s), 5.21(2H, br.s), 5.33(1H, 7-plet, J=6.62 Hz), 6.70(2H, s), 7.30(5H, s)

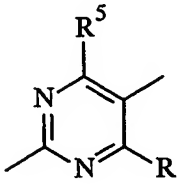
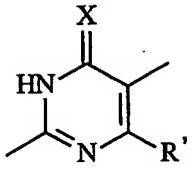
CLAIMS

1. An aminopyrimidine compound of the following formula (I).



(I)

wherein

Q is  or  ;

in which

R and R' are each optionally substituted aryl or heterocyclic group,

R^5 is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl, and

X is oxygen or sulfur;

R^1 is hydrogen, optionally substituted lower alkyl or cyclo(lower)alkyl which may be interrupted by an oxygen atom;

R^2 and R^3 are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

or a salt thereof.

2. A compound of claim 1,

wherein

R^1 is hydrogen, lower alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl or phenyl(lower)alkyl,

R^2 is hydrogen, lower alkyl, lower alkanoyl or optionally

substituted benzoyl,

R^3 is hydrogen, lower alkyl, phenyl, pyridinyl(lower)alkyl or $-CO-R^{31}$,

in which R^{31} is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)alkyl, optionally substituted lower alkoxy, optionally substituted phenyl or pyridinyl,

R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

R and R′ are each

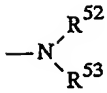
in which R^4 is hydrogen, halogen, hydroxy, lower alkyl, optionally substituted lower alkoxy, trihalo(lower)alkyl, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, and n is an integer from 1 to 3,

provided R^4 may be different from each other when n is 2 or 3; and

R^5 is hydrogen, halogen, lower alkyl, lower alkylthio, lower alkanoylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl,

$-O-R^{51}$,

in which R^{51} is hydrogen, optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or



in which R^{52} is hydrogen or lower alkyl;

R^{53} is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group,

R^{52} and R^{53} may be combined together with N atom to which they are attached to form N-containing heterocyclic group.

3. A compound of claim 2,

wherein

R^1 is hydrogen, methyl, ethyl, propyl, isopropyl, hydroxyisopropyl, methoxyisopropyl or benzyl;

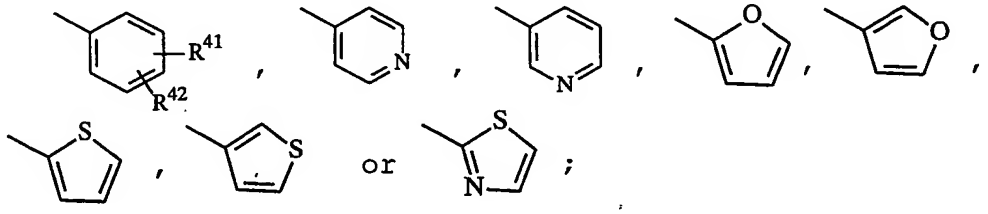
R^2 is hydrogen, methyl, acetyl, benzoyl, toluoyl, methoxybenzoyl, trifluoromethylbenzoyl, fluorobenzoyl or chlorobenzoyl;

R^3 is hydrogen, methyl, phenyl, pyridinylmethyl or $-CO-R^{31}$,

in which R^{31} is methyl, propyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, methoxy, methoxymethyl, trichloroethoxy, phenyl, tolyl, methoxyphenyl, trifluoromethylphenyl, fluorophenyl, chlorophenyl or pyridinyl, and

R^2 and R^3 may be combined together with N atom to which they are attached to form morpholino;

R and R' are each

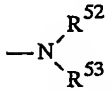


in which R^{41} and R^{42} are each independently hydrogen, fluoro, bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy, fluoropropoxy, dimethylaminoethoxy, morpholinylethoxy, methylthio, methylsulfinyl or methylsulfonyl; and

R^5 is hydrogen, fluoro, methyl, methylthio, acetylthio, phenylthio, methylsulfinyl, methylsulfonyl, $-O-R^{51}$,

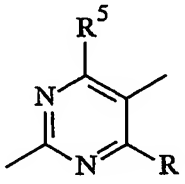
in which R^{51} is hydrogen, methyl, ethyl, propyl, isopropyl, allyl, propynyl, cyclobutyl, cyclohexyl, hydroxyethyl, methoxyethyl, carboxymethyl, aminoethyl,

dimethylaminoethyl, fluoroethyl, carbamoylmethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, cyclopropylcarbamoylmethyl, methoxycarbonylmethyl, tert-butoxycarbonylmethyl, acetylmethyl, benzoylmethyl, phenyl, benzyl, pyridinylmethyl, pyridinylethyl, tetrahydro-2H-pyranyl or 1,3(2H)-dioxoisoindolinylethyl, or



in which R^{52} is hydrogen or methyl,
R^{53} is hydrogen, methyl, ethyl, propyl, isopropyl, tert-butyl, allyl, cyclopropyl, hydroxyethyl, methoxyethyl, aminoethyl, dimethylaminoethyl, carbamoylmethyl, amidino, phenyl, benzyl, pyridinyl, pyridinylmethyl, furylmethyl or dimethylthiazolyl,
R^{52} and R^{53} may be combined together with N atom to which they are attached to form pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl or benzimidazolyl.

4. A compound of claim 1,
wherein
Q is

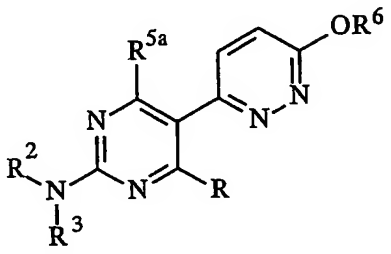


in which R and R^5 are each as defined in claim , and
R^1 is optionally substituted lower alkyl.

5. A compound of claim 4,
wherein
R^1 is lower alkyl or lower alkoxy(lower)alkyl, and
R^5 is hydrogen.

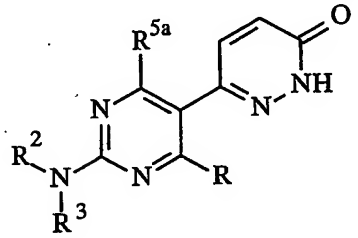
6. A compound of claim 5,
wherein
R^1 is lower alkyl, and
R^2 is hydrogen.

7. A process for the preparation of the aminopyrimidine compound of claim 1 or a salt thereof, which comprises,
(1) hydrolyzing a compound of the formula (II):



(II)

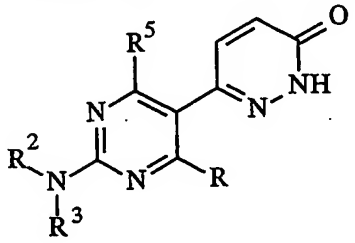
wherein
R, R^2 and R^3 are each as defined above,
R^{5a} is hydrogen, lower alkyl, optionally substituted hydroxy or optionally substituted amino, and
R^6 is lower alkyl, or a salt thereof,
to give a compound of the formula (Ia'):



(Ia')

wherein R, R^2, R^3 and R^{5a} are each as defined above or a salt thereof,

(2) reacting a compound of the formula (Ia):



(Ia)

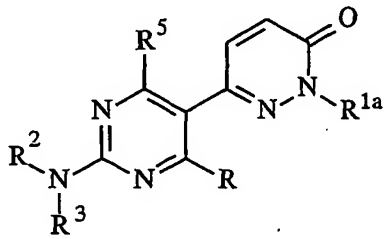
wherein R, R^2, R^3 and R^5 are each as defined above or a salt thereof, with a compound of the formula (III):

R^{1a}-Y^1 (III)

wherein R^{1a} is lower alkyl, cyclo(lower)alkyl which may be interrupted by an oxygen atom or aryl(lower)alkyl, and Y^1 is a leaving group,

or a salt thereof,

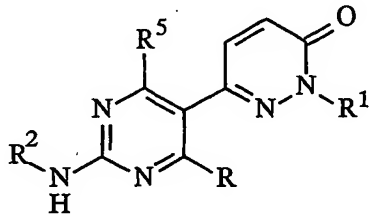
to give a compound of the formula (Ib):



(Ib)

wherein R, R^2, R^3, R^5 and R^{1a} are each as defined above or a salt thereof,

(3) reacting a compound of the formula (Ic):



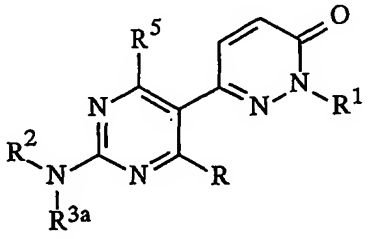
(Ic)

wherein R, R^1, R^2 and R^5 are each as defined above or a salt thereof, with a compound of the formula (IV):

R^{3a}-Y^2 (IV)

wherein R^{3a} is lower alkyl, acyl, aryl and aryl(lower)aryl, and Y^2 is a leaving group, or a salt thereof

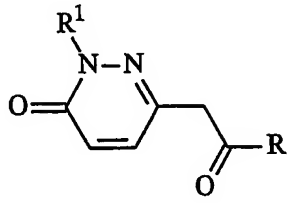
to give a compound of the formula (Id):



(Id)

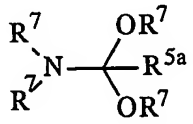
wherein R, R^1, R^2, R^5 and R^{3a} are each as defined above or a salt thereof,

(4) reacting a compound of the formula (V):



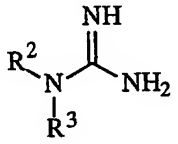
(V)

wherein R and R^1 are each as defined above or a salt thereof, with a compound of the formula:



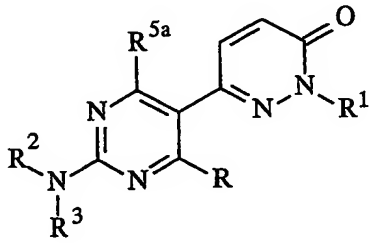
(VI)

wherein R^{5a} is as defined above,
and R^7 is lower alkyl or a salt thereof,
and further with a compound of the formula (VIII):



(VIII)

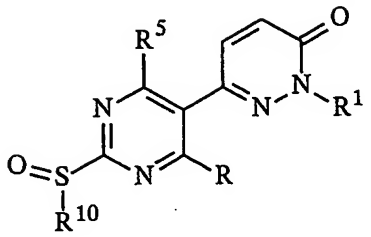
wherein R^2 and R^3 are each as defined above or a salt thereof, to give a compound of the formula (Ie):



(Ie)

wherein R, R^1, R^2, R^3 and R^{5a} are each as defined above or a salt thereof,

(5) reacting a compound of the formula (XXVI):

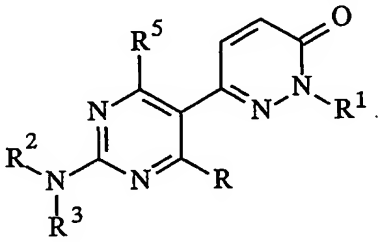


(XXVI)

wherein R, R^1 and R^5 are each as defined above, and
R^{10} is lower alkyl, or a salt thereof,
with a compound of the formula (XXVII):

R^2-NH-R^3 (XXVII)

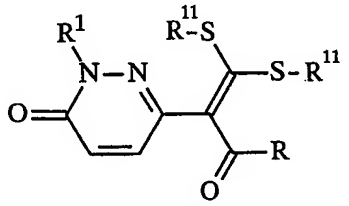
wherein R^2 and R^3 are each as defined above or a salt thereof,
to give a compound of the formula (I):



(I)

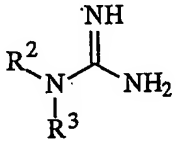
wherein R, R^1, R^2, R^3 and R^5 are each as defined above or a salt thereof,

(6) reacting a compound of the formula (XXXII):



(XXXII)

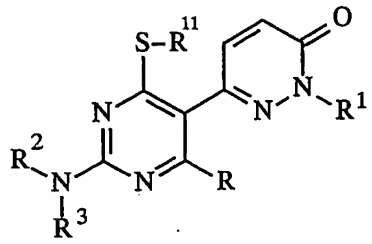
wherein R and R^1 are each as defined above, and
R^{11} is lower alkyl, or a salt thereof,
with a compound of the formula (VIII):



(VIII)

wherein R^2 and R^3 are each as defined above or a salt thereof,

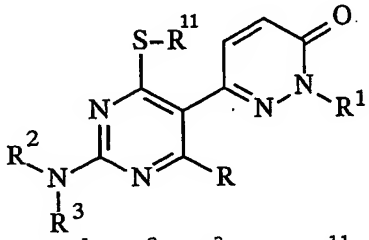
to give a compound of the formula (If):



(If)

wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

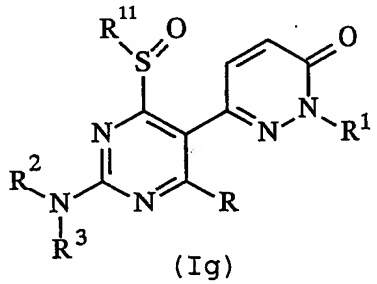
(7) oxidizing a compound of the formula (If):



(If)

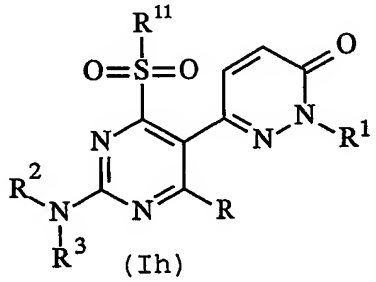
wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

to give compounds of the formula (Ig) and (Ih):



(Ig)

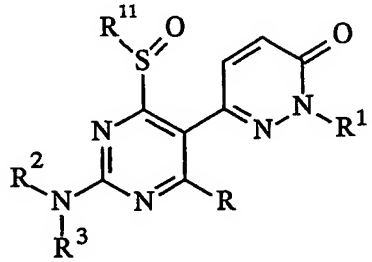
+



(Ih)

wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

(8) reacting a compound of the formula (Ig):



(Ig)

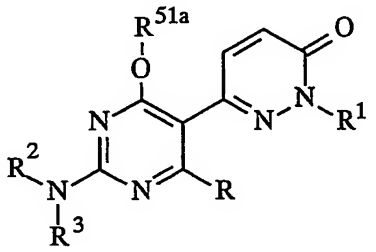
wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

with a compound of the formula (XXXIII):

R^{51a}-OH (XXXIII)

wherein R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or a salt thereof,

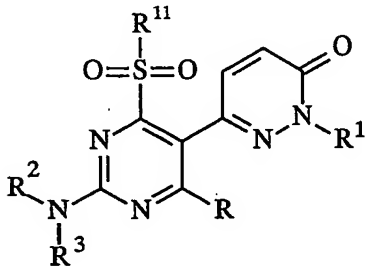
to give a compound of the formula (Ii):



(Ii)

wherein R, R^1, R^2, R^3 and R^{51a} are each as defined above or a salt thereof,

(9) reacting a compound of the formula (Ih):



(Ih)

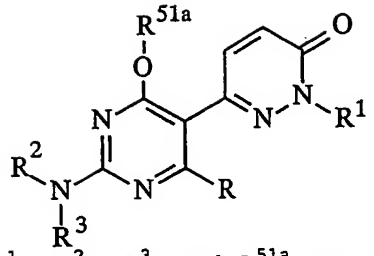
wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

with a compound of the formula (XXXIII):

R^{51a}-OH (XXXIII)

wherein R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or a salt thereof,

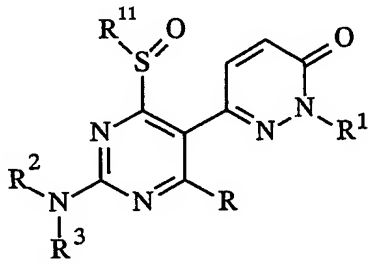
to give a compound of the formula (Ii):



(Ii)

wherein R, R^1, R^2, R^3 and R^{51a} are each as defined above or a salt thereof,

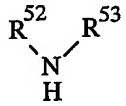
(10) reacting a compound of the formula (Ig):



(Ig)

wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,

with a compound of the formula (XXXIV):



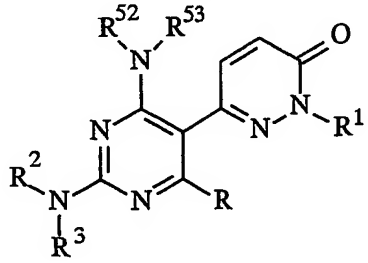
(XXXIV)

wherein R^{52} is hydrogen or lower alkyl,

R^{53} is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group, and R^{52} and R^{53} may be combined together with N atom to which they are attached to form N-containing heterocyclic group,

or a salt thereof,

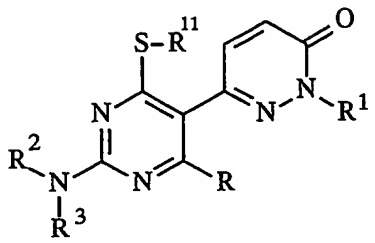
to give a compound of the formula (Ij):



(Ij)

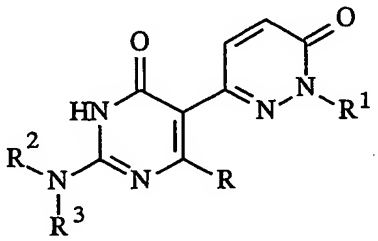
wherein R, R^1, R^2, R^3, R^{52} and R^{53} are each as defined above or a salt thereof,

(11) reacting a compound of the formula (If):



(If)

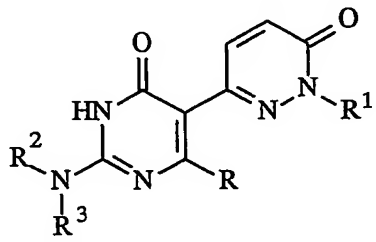
wherein R, R^1, R^2, R^3 and R^{11} are each as defined above or a salt thereof,
with urea hydrogen peroxide addition compound,
to give a compound of the formula (Ik):



(Ik)

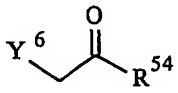
wherein R, R^1, R^2 and R^3 are each as defined above or a salt thereof,

(12) reacting a compound of the formula (Ik):



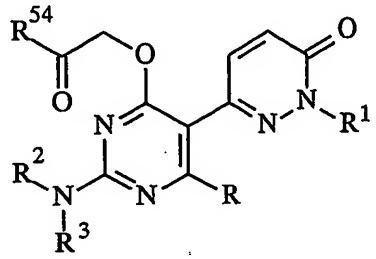
(Ik)

wherein R, R^1, R^2 and R^3 are each as defined above or a salt thereof,
with a compound of the formula (XXXV):



(XXXV)

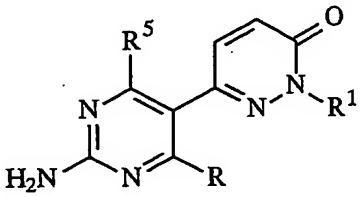
wherein R^{54} is lower alkyl, cyclo(lower)alkyl, lower alkoxy or aryl, and Y^6 is a leaving group,
or a salt thereof,
to give a compound of the formula (Il):



(Il)

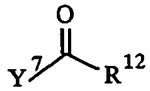
wherein R, R^1, R^2, R^3 and R^{54} are each as defined above or a salt thereof,

(13) reacting a compound of the formula (Im):



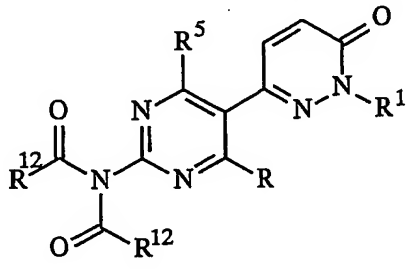
(Im)

wherein R, R^1 and R^5 are each as defined above or a salt thereof, with a compound of the formula (XXXVI):



(XXXVI)

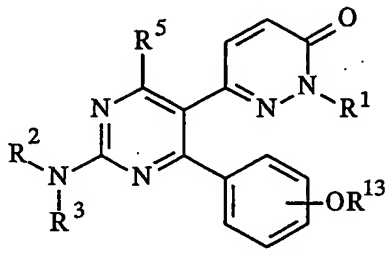
wherein R^{12} is optionally substituted aryl or lower alkoxy, and Y^7 is a leaving group,
or a salt thereof,
to give a compound of the formula (In):



(In)

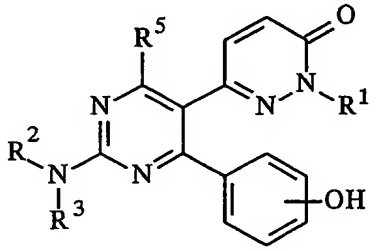
wherein R, R^1, R^2, R^3 and R^{54} are each as defined above or a salt thereof,

(14) reacting a compound of the formula (Io):



(Io)

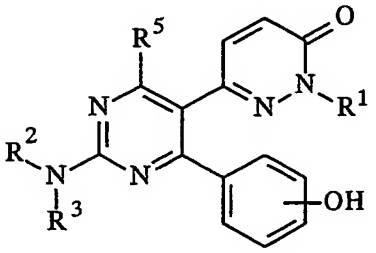
wherein R^1, R^2, R^3 and R^5 are each as defined above, and R^{13} is lower alkyl, or a salt thereof,
to give a compound of the formula (Ip):



(Ip)

wherein R^1, R^2, R^3 and R^5 are each as defined above or a salt thereof,

(15) reacting a compound of the formula (Ip):

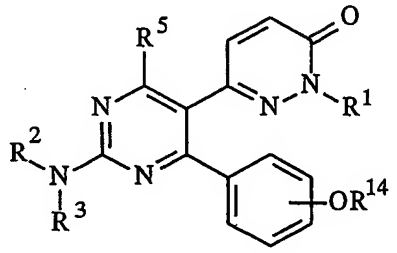


(Ip)

wherein R^1, R^2, R^3 and R^5 are each as defined above,
or a salt thereof,
with a compound of the formula (XXXVII):

Y^8-R^{14} (XXXVII)

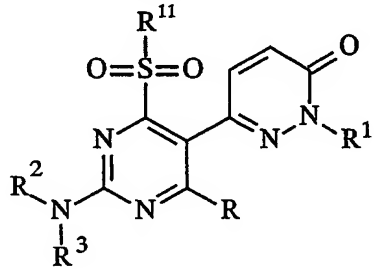
wherein R^{14} is optionally substituted lower alkyl, and
Y^8 is a leaving group, or a salt thereof,
to give a compound of the formula (Iq):



(Iq)

wherein R^1, R^2, R^3, R^5 and R^{14} are each as defined above or a salt thereof.

(16) reacting a compound of the formula (Ih):

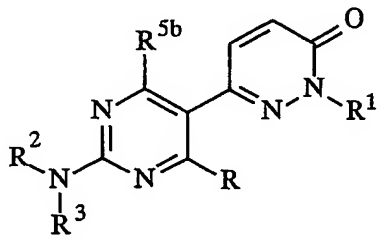


(Ih)

wherein R, R^1, R^2, R^3 and R^{11} are each as defined above, or a salt thereof,
with a compound of the formula (XXXVIII):

$$Y^9\text{-}M\text{-}R^{5b} \quad \text{(XXXVIII)}$$

wherein R^{5b} is lower alkyl, Y^9 is a leaving group and M is metal, or a salt thereof,
to give a compound of the formula (Ir):



(Ir)

wherein R, R^1, R^2, R^3 and R^{5b} are each as defined above or a salt thereof.

8. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

9. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris, which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

10. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, Meniere's syndrome and cerebral infarction, which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

12. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an adenosine antagonist.

13. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an A_1 receptor and A_2 receptor dual antagonist.

14. A process for preparing a pharmaceutical composition which comprises admixing the compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

15. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine antagonist is therapeutically effective.

16. A method for evaluation of adenosine antagonism which comprises use of compound of claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/13796

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D409/14 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 848 000 A (TANABE SEIYAKU CO) 17 June 1998 (1998-06-17) claims 1,19,20; examples 21,34 ---	1,8,9
A	EP 0 748 805 A (TANABE SEIYAKU CO) 18 December 1996 (1996-12-18) claims 1,37,38; example 49 ---	1,8,9
A	WO 91 12251 A (CHUGAI PHARMACEUTICAL CO LTD) 22 August 1991 (1991-08-22) abstract; claims 1,3 ---	1,8,9
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 05, 14 September 2000 (2000-09-14) -& JP 2000 063275 A (TANABE SEIYAKU CO LTD), 29 February 2000 (2000-02-29) abstract; example 21 ---	1,8,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2003	28/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/13796

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 13, 30 November 1998 (1998-11-30) -& JP 10 226647 A (TANABE SEIYAKU CO LTD), 25 August 1998 (1998-08-25) abstract; example 49	1,8,9
A	M. YAMAGUCHI ET AL: "Novel Antiasthmatic Agents with Dual Activities of Thromboxane A2 Synthetase Inhibition and Bronchodilation. 2. 4-(3-Pyridyl)-1(2H)-phthalazinones" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 25, 1993, pages 4061-4068, XP001151968 table I	1,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/13796

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9, 10 and possibly 16 are directed to a method of treatment or a diagnostic method of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/13796

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